Unit I

General Pharmacology

1. Principles of Pharmacology, Evidence-based Medicine and Routes of Drug Administration
2. Pharmacokinetics
3. Pharmacodynamics
4. Adverse Drug Reactions, Pharmacovigilance and Drug Interactions
5. Drug Nomenclature, Drug Development, Drug Regulations, Essential Medicines, Prescriptions and Related Topics

CHAPTER 1

Principles of Pharmacology, Evidence-based Medicine and Routes of Drug Administration

Competency achievement: The student should be able to:

PH 1.1 Define and describe the principles of pharmacology and pharmacotherapeutics.[1]

PH 1.2 Describe the basis of evidence-based medicine and therapeutic drug monitoring.[2]

Pharmacology is the science that deals with the study of drugs and their interaction with the living systems. The word pharmacology is derived from the Greek word—***Pharmacon*** meaning an active principle and ***logos*** meaning a discourse.

HISTORICAL ASPECTS

The useful and toxic effects of many plant and animal products were known to man since ancient times. In fact, there has been a quest for drugs and remedies since the existence of mankind itself.

In early days, there was a close relationship between religion and the treatment of diseases. The knowledge of the use of drugs often rested with the priest or holyman. Drugs were thought to be magical in their actions. Several cultures like the Chinese, Greek, Indian, Roman, Persian, European and many others contributed a great deal to the development of medicine in early times. The drug prescriptions included preparations from herbs, plants, animals and minerals. However, written information on remedies used in early times is lacking.

The Indian and the Chinese writings are amongst the oldest written material in medicine. India's earliest pharmacological writings are from the 'Vedas'. Rigveda (3000 BC) has description of some medicines. An ancient Indian physician Charaka, and then, Sushruta and Vagbhata, described many herbal preparations included in **'Ayurveda'** (meaning the science of life). Indians practiced vaccination as early as 550 BC.

'Pen Tsao' the Chinese materia medica was written as early as 1700 BC and it contained classification of medicinal plants and some preparations of plants, metals and animals.

The Egyptian medical papyri (1600 BC) described several preparations. The largest of them, Ebers Papyrus lists some 800 preparations.

The Greeks studied the toxic effects of various plant extracts. Their contribution to the growth of modern medicine is significant. **Hippocrates** (460–377 BC), a Greek physician, studied the cause of disease and wrote on the ethics of medicine and recommended judicious use of drugs. Galen (130–201 BC), also a Greek physician, practiced in Rome and put forth a doctrine that diseases are due to an imbalance of fluids—blood, phlegm, black bile and yellow bile. He believed that drugs had some properties like warmth, coldness, dryness or humidity and also thought that it is beneficial to use a combination of drugs to obtain these effects.

In the Middle Ages, many herbal gardens were cultivated by the monasteries. **Paracelsus** the **'Grandfather of Pharmacology'** born in Switzerland was the son of a physician. He

opined that complicated mixture of drugs should not be used and also wrote, "all drugs are poisons—it is only the dose which makes a thing a poison." This statement holds good even today.

Though medicine developed simultaneously in several countries, the spread of knowledge was limited because of poorly developed communication across the world. By the beginning of the first century, it was realized that there was a need to standardize the method of obtaining uniform medical preparations.

James Gregory (1735–1821 AD) recommended certain dangerous measures like blood letting, use of emetics and purgatives in the treatment of diseases—such measures were often fatal. He meant to induce other suffering to relieve pain/suffering and this was probably the basis of the word '**allopathy**' meaning 'the other suffering'. This word, still being used for the modern system of medicine, is a misnomer. **Homeopathy** meaning 'similar suffering' was introduced by **Samuel Hahnemann.** The principles of this system include 'like cures like' and 'dilution enhances the potency of drugs'. Various traditional systems of medicine were practiced in different parts of the world like Homeopathy, Ayurveda, Unani, Siddha system and Allopathy.

Thus several systems of medicine were introduced, of which only a few survived. The basic reason for the failure of these systems is that man's concepts about diseases were incorrect and baseless in those days. By the end of the 17th century, the importance of experimentation, observation and scientific methods of study became clear. **Francois Magendie** and **Claude Bernard** popularized the use of animal experiments to understand the effects of drugs. Simultaneous development of other branches of science, viz. botany, zoology, chemistry and physiology helped in the better understanding of pharmacology.

By the nineteenth century, methods for isolation of drugs were developed. **Rudolph Bucheim** (1820–1879) set up the first laboratory in his home at Dorpat Estonia in 1847 exclusively meant for research on drugs. **Oswald Schmiedeberg** (1838–1921), a student of Bucheim, conducted extensive research on drugs, trained 120 students and wrote a medical textbook. He has been called '**Father of Pharmacology**' for his contribution and was the most prominent pharmacologist of the 19th century.

With the growth of science and the development of scientific methods of research, treatment of diseases now relies largely on scientific evidence. Well-designed multicentric trials involving a fair number of participants are required to prove the safety and benefits of a drug in a given condition before it can be used in general population making the modern system **evidence-based medicine** (*see* page 6).

The last century has seen a rapid growth of the subject with several new drugs, new concepts and techniques being introduced. We now know much more about receptors and molecular mechanisms of action of many drugs. Several diseases, which were considered incurable and fatal, can now be completely cured with just a few tablets.

TERMINOLOGY

Drug (*Drogue*—a dry herb in French) is a substance used in the diagnosis, prevention or treatment of a disease. **WHO definition**, "A drug is any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient."

Pharmacokinetics is the study of the absorption, distribution, metabolism and excretion of drugs, i.e. what the body does to the drug (in Greek *Kinesis = movement*).

Pharmacodynamics is the study of the effects of the drugs on the body and their mechanisms of action, i.e. what the drug does to the body.

Therapeutics deals with the use of drugs in the prevention and treatment of disease.

Pharmacoeconomics deals with the cost, i.e. economic aspects of drugs used therapeutically.

Pharmacogenetics (and pharmacogenomics) is the science that deals with the study of genetic basis for variation in drug responses (*see* page 54).

Pharmacoepidemiology is the study of both the useful and adverse effects of drugs on large number of people.

Pharmacovigilance is related to the detection, assessment, understanding and prevention of adverse effects of drugs (*see* page 65).

Toxicology deals with the adverse effects of drugs and also the study of poisons, i.e. detection, prevention and treatment of poisoning *(Toxicon = poison in Greek)*.

Chemotherapy is the use of drugs and chemicals for the treatment of infections. The term now also includes the use of chemical compounds to treat malignancies.

Essential medicines are those that satisfy the healthcare needs of majority of the population and should be available at all times in adequate amounts and in the appropriate dosage forms (*see* page 74) as defined by the WHO.

Orphan drugs are drugs to be used for prevention and treatment of rare diseases.

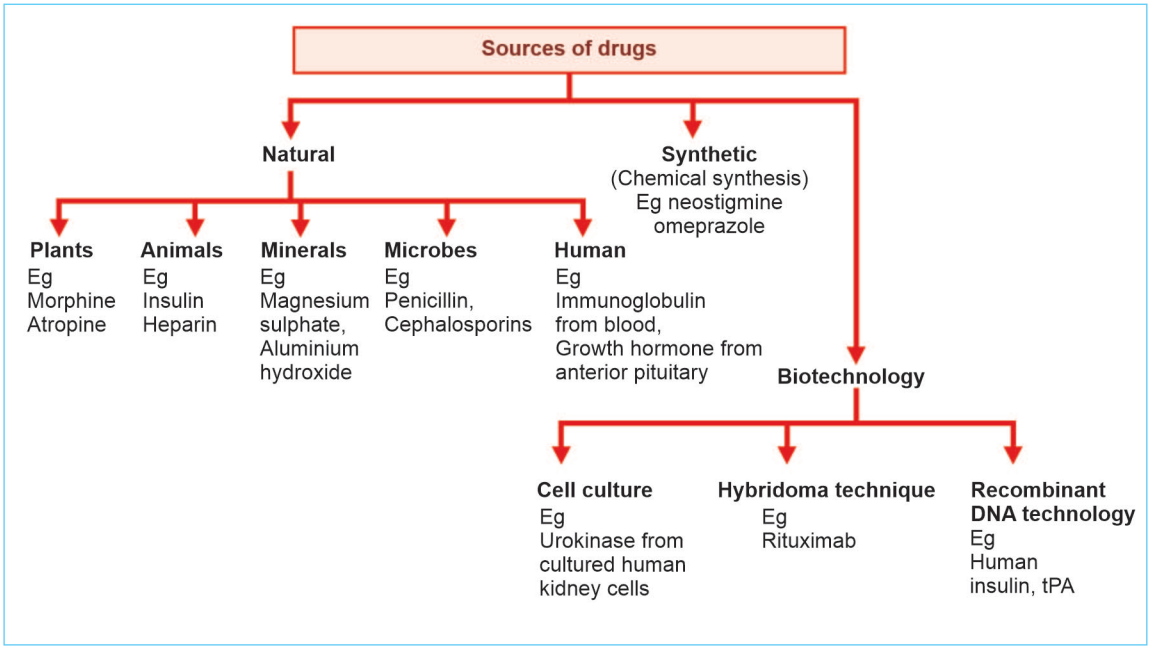
Pharmacopoeia is the official publication containing information on drugs (*see* page 72).

Pharmacy is the science of identification, compounding and dispensing of drugs. It also includes collection, isolation, purification, synthesis and standardization of medicinal substances.

Chronopharmacology is the science that involves the correlation of drug effects to the circadian rhythm to obtain optimum therapeutic effect and minimize the adverse effects, e.g. bronchospasm usually occurs at night. Blood pressure rises at dawn and dusk and is the lowest at midnight (*see* page 73). **Chronotherapy** is the administration of drugs to match the circadian rhythm. ***Chronobiotics*** are drugs that can be used to modify or reset the circadian rhythm. They find application mostly in conditions like sleep disorders and jet lag.

SOURCES OF DRUGS

The sources of drugs could be natural, or synthetic and biotechnology.



A. Natural Sources

Drugs can be obtained from:

1. *Plants*, e.g. atropine, morphine, quinine, digoxin, pilocarpine, and physostigmine.
2. *Animals*, e.g. insulin, heparin, gonadotrophins and antitoxic sera.
3. *Minerals*, e.g. magnesium sulphate, aluminium hydroxide, iron, gold, sulphur and radioactive isotopes.
4. *Microorganisms*—antibacterial agents are obtained from some bacteria and fungi, e.g. penicillin, cephalosporins, tetracyclines.
5. *Human*—some drugs are obtained from human source, e.g. immunoglobulins from blood, growth hormone from anterior pituitary and chorionic gonadotrophins from the urine of pregnant women.

B. Synthetic

Most drugs used now are synthetic. They may be manufactured in large quantities and therefore can be less expensive, e.g. quinolones, omeprazole, sulfonamides, pancuronium and neostigmine.

C. Biotechnology

Use of biotechnology in the production of drugs and biologicals has helped to treat many ailments which were once incurable. It has been possible to synthesize many congeners with minor modifications. For example:

- By **cell cultures,** e.g. urokinase from cultured human kidney cells.
- By **recombinant DNA technology,** e.g. human insulin, tissue plasminogen activator, haematopoietic growth factors like erythropoietin, filgrastim and sargramostim.
- By **hybridoma technique,** e.g. monoclonal antibodies like rituximab.

Competency achievement: The student should be able to:

PH 1.2 Describe the basis of evidence-based medicine and therapeutic drug monitoring.[3]

Evidence-based Medicine (EBM)

With the growth of science and the development of scientific methods of research, treatment of diseases now relies largely on scientific evidence obtained from studies.

Definition: EBM is applying the best evidence that can be found in the medical literature to medical practice, resulting in the best possible patient care.

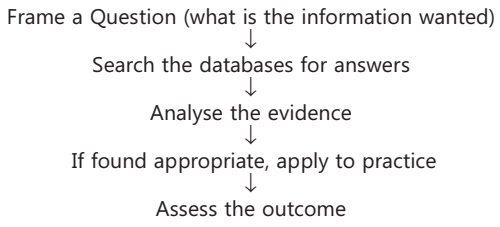
Need for EBM: There is high degree of variation in medical practice despite doctors being trained with the same curriculum. With the medical care getting more complex and expensive, it is important to know the best possible care and whenever possible cost-effective treatment.

EBM has 3 components—acquiring information, critical analyse of it and then applying the information to patient care.

Searching the medical literature for best evidence requires good searching skills using medical informatics. It can be time consuming, but many database providers are developing search engines to quickly find reliable and valid information.

The most complex part of the process of EBM is the critical analysis of the medical literature. **Meta-analysis or systematic review** is a relatively new technique that combines many studies on a given topic and analyses them. The **TRIP** database can be used for a systematic search of nearly 100 evidence-based databases including Medline and Cochrane library and can provide a summary of the results.

Steps in EBM



Lastly, effectiveness of the practice should also be evaluated before it is incorporated into routine practice.

EBM is a relatively new concept but is now largely popular. Evidence based practices can be more or less expensive than current practices, but they are better.

Therapeutic Drug Monitoring is the use of plasma drug levels to guide treatment (*see* page 38).

Competency achievement: The student should be able to:
PH 1.3 Enumerate and identify drug formulations and drug delivery systems.[4]

DRUG FORMULATIONS AND DOSAGE FORMS

Drug formulation is the drug dosage form in which the drug is administered. The right dosage form is important to deliver the drug to the site of action. Drugs may be administered in solid or liquid dosage forms (Table 1.1).

Drug Delivery Systems

Appropriate drug delivery systems are important to attain right drug levels at the site of action. In order to improve drug delivery, to prolong the duration of action and thereby improve patient compliance, **special drug delivery systems** are being tried. Drug targeting, i.e. to deliver drugs at the site where it is required to act is also being aimed at, particularly for anticancer drugs. Some such systems are:

***a. Ocusert*:** Ocusert systems are thin elliptical units that contain the drug in a reservoir which slowly releases the drug through a membrane by diffusion at a steady rate, e.g. pilocarpine ocusert used in glaucoma is placed under the lid and can deliver pilocarpine for 7 days.

***b. Progestasert*:** Progestasert is inserted into the uterus where it delivers progesterone constantly for over one year.

c. Transdermal adhesive units: *See* page 15

***d. Prodrug*:** Prodrug is an inactive form of a drug which gets metabolized to the active derivative in the body. Using a prodrug may overcome some of the disadvantages of the conventional forms of drug administration, as follows:

Advantages

1. *Increase availability at the site*, e.g. dopamine does not cross the BBB; levodopa, a prodrug, crosses the BBB and is then converted to dopamine in the CNS.
2. *Prolong duration of action:* Prodrugs may be used to achieve longer duration of action, e.g. bacampicillin (a prodrug of ampicillin) is longer-acting than ampicillin.
3. *Improve tolerability*, e.g. cyclophosphamide, an anticancer drug, gets converted to its active metabolite aldophosphamide in the liver. This allows oral administration of cyclophosphamide without causing much gastrointestinal toxicity.
4. *Drug targeting:* Zidovudine is taken up by the virus infected cells and gets activated in these cells. This results in selective toxicity to infected cells.
5. *Improve stability:* A prodrug may be more stable at gastric pH, e.g. aspirin is converted to salicylic acid which is the more stable active drug and aspirin is also better tolerated than salicylic acid.
6. *Reduce side effects:* Prodrug could be used to lower side effects—for example, bacampicillin, a prodrug of ampicillin, is better absorbed and therefore causes less diarrhoea.

Disadvantages

1. Prodrugs are likely to have a slower onset of action and therefore are not suitable in emergencies.
2. In presence of liver diseases prodrugs may not be activated to attain therapeutic levels (Mnemonic *see* page 17).

***e. Osmotic pumps*:** These are small tablet-shaped units containing the drug and an osmotic substance in two different chambers. The tablet is coated with a semipermeable membrane in which a minute laser-drilled hole is made. When the tablet is swallowed

Table 1.1: Drug formulations and dosage forms

Drug dosage forms

Solids

Powders are solid dosage forms in a finely divided state. They may be used for internal administration or for external application. e.g: Neomycin powder

Capsules are solid dosage forms in which the drug is enclosed in a tasteless, hard or soft soluble shell made up of a suitable form of gelatin. They may be spherical, ovoid or cylindrical; Spherical capsules are known as 'pearls'.

Tablets are solid dosage forms of medicaments prepared by molding or by compression.

Lozenges are solid dosage forms meant for slow dissolution in the mouth.

Dry syrups are powders which are to be made into solution before use. Drugs which are not stable in solution are dispensed as dry syrups, eg: Antibiotics including amoxicillin, erythromycin, cephalexin, ampicillin.

Liquids

Solutions are liquid dosage forms prepared by dissolving a solute in a solvent. eg: Potassium permanganate solution.

Mixture is a liquid preparation containing two or more substances intended for oral administration.

Elixirs are clear, pleasantly flavored, sweetened liquid preparations for oral administration. eg: Chlorpheniramine elixir, paracetamol elixir.

Syrups are sweet, viscous, aqueous preparations of sugars in an aqueous vehicle.

Suspensions are liquid dosage forms in which finely divided solid particles (0.5 to 5.0 microns) are suspended in a liquid or semisolid vehicle using a suspending agent. Eg: Barium sulphate suspension, kaolin suspension

Linctuses are sweet, viscous liquid preparations used for the treatment of cough. Linctuses are swallowed slowly in small doses without addition of water, eg: Codeine linctus, noscapine linctus.

Gargles and mouthwashes: Gargles are aqueous solutions used for the prevention or treatment of throat infections. Mouthwashes are aqueous solutions for deodorizing and refreshing the oral cavity.

Tinctures are alcoholic liquid preparations prepared by dissolving the corresponding liquid extract in solvents, eg: Belladonna tincture, opium tincture.

Emulsions are liquid dosage forms in which two immiscible liquids are made miscible with the help of an emulsifying agent. Labeled with 'shake the bottle before use. Examples: Phenolphthalein emulsion.

Liniments are liquid or semiliquid preparations meant for external application to the skin with friction but should not be applied to the broken skin.

Lotions are liquid suspensions meant for external application without friction.

Others

1. **Aerosols:** Pressurized dosage forms in which the liquid or solid drugs are dissolved or suspended in gas. They bring about fine dispersion of liquid (mist) or solid particles of size less than 50 microns in diameter, eg: Drugs for bronchial asthma, deodorant sprays, cosmetic hair sprays.
2. **Semisolids:** Ointments are soft semisolid preparations meant for external application to the skin or mucous membrane. Creams are viscous semisolid emulsions meant for application to skin. Creams are lighter than ointments.
3. **Enemas** are aqueous or oily solutions or suspensions intended for introduction into the rectum.
4. **Injections** are liquid preparations containing one or more medicaments dissolved or suspended in a suitable vehicle and are meant for introduction into the body tissues with the help of a syringe and needle, eg: Ampicillin injection, dextrose intravenous infusion.
5. **Suppositories** are special shaped solid dosage forms for insertion into body cavities other than mouth. They may be inserted into rectum, vagina or urethra, eg: Clotrimazole suppository.

and reaches the gut, water enters into the tablet through the semipermeable membrane. The osmotic layer swells and pushes the drug slowly out of the laser-drilled orifice. This allows slow and constant delivery of the drug over a long period of time. It is also called **gastrointestinal therapeutic system** (GITS). Some drugs available in this formulation are iron and prazosin.

f. Computerised miniature pumps: These are programmed to release drugs at a definite rate either continuously as in case of insulin or intermittently in pulses as in case of GnRH.

Various methods of drug targeting are tried especially for anticancer drugs to reduce toxicity.

g. Targeted drug delivery systems: In the last decade, efforts have been made to deliver drugs to the site of action. Such drug targeting is the dream of any pharmacologist, since it would mean a remarkable progress in therapeutics. Drug targeting largely reduces the adverse drug reactions because the required amount of the drug will be delivered at the required site of action.

Some of the targeted delivery systems currently available are:

(i) *Liposomes* are phospholipids suspended in aqueous vehicles to form minute vesicles. They are used as carriers for both water-soluble and lipid-soluble substances as they can be entrapped in the aqueous spaces or within the lipid layer itself. For example, a lipid is hydrated with an aqueous solution of the drug.

Though liposomes can be given both orally and parenterally, IV route is the most common. Small liposomes are taken up by the reticuloendothelial cells while larger ones are deposited in the lungs and are also concentrated in malignant tumours. Thus site-specific delivery of drugs may be possible with the help of liposomes. Liposomes are used in the treatment of cancers, systemic fungal infections, diabetes mellitus and in heavy metal poisoning. Examples of some liposomes available are doxorubicin, cytarabin, cisplatin and irinotecan.

(ii) *Monoclonal antibodies* against the tumour-specific antigens are used to deliver anticancer drugs to specific tumour cells.

(iii) *Nanoparticles:* The drug is encapsulated or dissolved in the nanoparticle (NP) matrix to obtain nanocapsules or nanoparticles. The size of the nanoparticles vary from 10 to 1000 nm and are biogradable. They can be used to deliver the anticancer drugs to the cancer tissue in order to improve efficacy and reduce toxicity.

(iv) *Polymer-based drug delivery:* Polymers have been used in transdermal drug delivery systems. Polymers are used for coating as in enteric-coated capsules and drug eluting stents. Drugs are also designed to be delivered directly to the colon in ulcerative colitis and inflammatory bowel disease.

(v) *Drug eluting stents* are devices consisting of a metallic stent (tubular mesh-like device) coated with a drug on a polymer coating. The drug may be sirolimus or paclitaxel. The drug is gradually released over 4–6 weeks and prevents the proliferation of vascular smooth muscles and endothelial cells over the stent placed.

ROUTES OF DRUG ADMINISTRATION

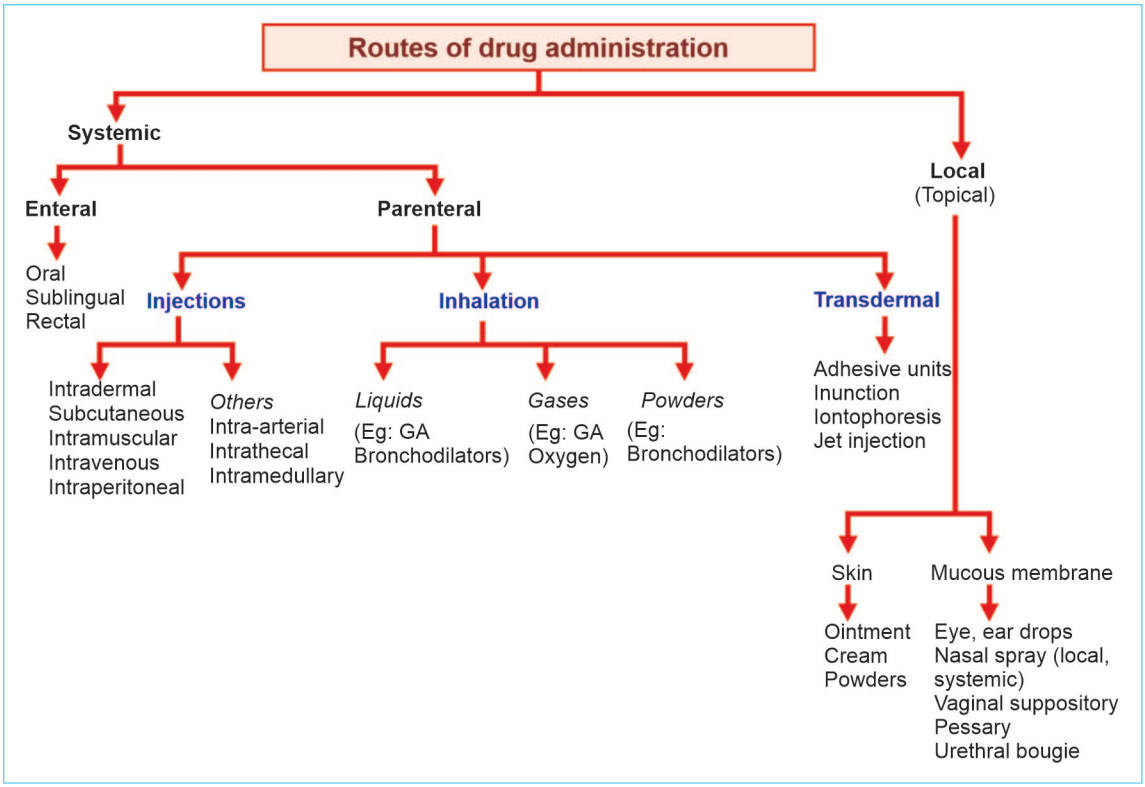
Competency achievement: The student should be able to:

PH 1.11 Describe various routes of drug administration, e.g. oral, SC, IV, IM, SL .[5]

Drugs may be administered by various routes. The choice of the route in a given patient depends on the properties of the drug and the patient's requirements. A knowledge of the advantages and disadvantages of the different routes of drug administration is essential for appropriate use of drugs.

The routes can be broadly divided into:

- Systemic routes
- Local/topical routes.



SYSTEMIC ROUTES

Enteral Routes

Enteral routes include oral, sublingual and rectal routes.

1. Oral route is the most commonly used, oldest and safest route of drug administration. The large surface area of the gastrointestinal tract, the mixing of its contents and the differences in pH at different parts of the gut facilitate effective absorption of the drugs given orally.

However, the acid and enzymes secreted in the gut and the biochemical activity of the bacterial flora of the gut can destroy some drugs before they are absorbed.

Advantages

- Safest route
- Most convenient
- Most economical
- Drugs can be self-administered
- Non-invasive route.

Disadvantages

- ***Slow action:*** Onset of action is slower as absorption needs time—hence particularly not suitable for emergencies.
- ***Drug properties:*** Irritant and unpalatable drugs cannot be administered.
- ***Poor absorption:*** Some drugs may not be absorbed due to certain physical and chemical characteristics, e.g. streptomycin is not absorbed orally.
- ***GI irritation:*** Irritation to the gastrointestinal tract may lead to vomiting.
- ***Unpredictable absorption:*** There may be irregularities in absorption.
- ***Metabolism:*** Some drugs may be destroyed by gastric juices, e.g. insulin.

- ***Unsuitable situations:*** Oral preparations cannot be given to unconscious and uncooperative patients.
- ***First pass effect:*** Some drugs may undergo extensive first pass metabolism in the liver.

To overcome some of the disadvantages, irritants are given in capsules, while bitter drugs are given as sugar-coated tablets. Sometimes drugs are coated with substances like synthetic resins, gums, sugar, colouring and flavouring agents, making them more acceptable.

Enteric-coated Tablets

Some tablets are coated with substances or polymers like cellulose-acetate, phthalates, gluten, shellac, etc. which are not digested by the gastric acid but get disintegrated in the alkaline juices of the intestine. The choice of the polymer and the thickness of coating influence the dissolution of the coat in the intestines. Enteric coating will:

- Prevent gastric irritation
- Avoid destruction of the drug by the stomach
- Provide higher concentration of the drug in the small intestine
- Retard the absorption, and thereby prolong the duration of action.

However, if the coating is inappropriate, the tablet may be expelled without being absorbed at all.

Similarly, controlled-release or sustained-release preparations are designed to prolong the rate of absorption and thereby the duration of action of the drugs (Fig. 1.1). This is useful for short-acting drugs. In newer controlled release formulations, the tablet is coated with a semipermeable membrane through which water enters and displaces the drug out.

Advantages

- Frequency of administration may be reduced.

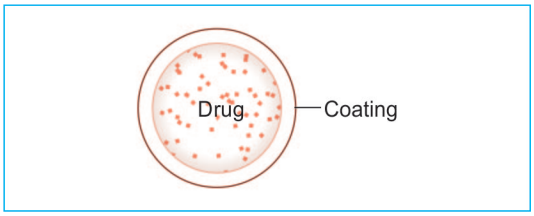


Fig. 1.1: Sustained release preparation. Dissolution of coating depends on the thickness and stability of the coat

- Therapeutic concentrations may be maintained specially when nocturnal symptoms are to be treated.

Disadvantages

- There may be 'failure of the preparation' resulting in release of the entire amount of the drug in a short time, leading to toxicity.
- Enteric coated tablets are more expensive.

Certain precautions are to be taken during oral administration of drugs—capsules and tablets should be swallowed with a glass of water with the patient in upright posture either sitting or standing. This facilitates passage of the tablet into the stomach and its rapid dissolution. It also minimises the chances of the drug getting into the larynx or behind the epiglottis. Recumbent patient should not be given drugs orally as some drugs may remain in the oesophagus due to the absence of gravitational force facilitating the passage of the drug into the stomach. Such drugs can damage the oesophageal mucosa, e.g. iron salts, tetracyclines.

2. Sublingual

Here, the tablet or pellet containing the drug is placed under the tongue. As the drug dissolves, it is absorbed across the sublingual mucosa, e.g. nitroglycerin, nifedipine, buprenorphine. The tablet may also be crushed in the mouth but not swallowed and the contents are absorbed across the buccal mucosa. The formulation should be so

designed that it quickly dissolves in the saliva. The buccal mucosa is rich in blood supply. This allows quick absorption of the drug.

Advantages

- Absorption is rapid—within minutes the drug reaches the circulation.
- First pass metabolism is avoided because the drug directly reaches the systemic circulation.
- After the desired effect is obtained, the drug can be spat out to avoid the unwanted effects.

Disadvantages

- Buccal ulceration can occur.
- Lipid-insoluble drugs, drugs of higher molecular weight, irritant and unpalatable drugs cannot be given by this route.

3. Rectal

Rectum has a rich blood supply and drugs can cross the rectal mucosa to be absorbed for systemic effects. Drugs absorbed from the upper part of the rectum are carried by the superior haemorrhoidal vein to the portal circulation (can undergo first pass metabolism), while that absorbed from the lower part of the rectum is carried by the middle and inferior haemorrhoidal veins to the systemic circulation. Drugs like indomethacin, chlorpromazine, diazepam and paraldehyde can be given rectally.

Some irritant drugs are given rectally as suppositories.

Advantages

- Gastric irritation is avoided.
- Can be administered by unskilled persons.
- Useful in geriatric patients; patients with vomiting, those unable to swallow and after gastrointestinal surgery.
- Also useful in unconscious patients.

Disadvantages

- Irritation of the rectum can occur.
- Absorption may be irregular and unpredictable.

Drugs may also be given by rectal route as enema.

Enema is the administration of a drug in a liquid form into the rectum. Enema may be evacuant or retention enema.

Evacuant enema: In order to empty the bowel, about 600 ml of soap water is administered per rectum. Water distends and thus stimulates the rectum while soap lubricates. Enema is given prior to surgeries, obstetric procedures and radiological examination of the gut.

Retention enema: The drug is administered with about 100 ml of fluids and is retained in the rectum for local action, e.g. prednisolone enema in ulcerative colitis.

Parenteral Routes

Routes of administration other than the enteral (intestinal) route are known as parenteral routes. Here the drugs are directly delivered into the tissue fluids or blood.

Advantages

- Action is more rapid and predictable than oral administration.
- These routes can be employed in an unconscious or uncooperative patient.
- Gastric irritants can be given parenterally and, therefore, irritation to the gastrointestinal tract can be avoided.
- It can be used in patients with vomiting or those unable to swallow.
- Digestion by the gastric and intestinal juices and the first pass metabolism are avoided.

Therefore, in emergencies, parenteral routes are very useful for drug administration as the action is rapid and predictable and are useful even in unconscious patients.

Disadvantages

- Asepsis must be maintained
- Injections may be painful
- More expensive, less safe and inconvenient
- Injury to nerves and other tissues may occur.

Parenteral routes include:

1. Injections
2. Inhalation
3. Transdermal route

1. Injections

Injections are given with the help of syringe and needle.

Intradermal

The drug is injected:

- Into the layers of the skin raising a bleb, e.g. BCG vaccine, tests for allergy.
- By multiple punctures of the epidermis through a drop of the drug, e.g. smallpox vaccine. Only a small quantity can be administered by this route and it may be painful.

Subcutaneous (SC) Injection

Here the drug is deposited in the SC tissue, e.g. insulin, heparin. As this tissue is less vascular, absorption is slow and largely uniform, making the drug long-acting. It is reliable and patients can be trained for self-administration. Absorption can be enhanced by the addition of the enzyme hyaluronidase.

Disadvantages

- As SC tissue is richly supplied by nerves, irritant drugs cannot be injected because they can cause severe pain.
- In shock, absorption is not dependable because of vasoconstriction.
- Repeated injections at the same site can cause lipoatrophy resulting in erratic absorption.

Hypodermoclysis is the subcutaneous administration of large volumes of saline employed in paediatric practice.

Drugs can also be administered subcutaneously as:

i. *Dermojet:* In this method, a high velocity jet of drug solution is projected from a fine orifice using a 'gun'. The solution gets deposited in the SC tissue from where it is absorbed. As needle is not required, this method is painless. It is suitable for vaccines.

ii. *Pellet implantation:* Small pellets packed with drugs are implanted subcutaneously. The drug is slowly released for weeks or months to provide constant blood levels, e.g. testosterone, desoxycorticosterone acetate (DOCA).

iii. *Sialistic implants:* The drug is packed in sialistic tubes and implanted subcutaneously. The drug gets absorbed over months to provide constant blood levels, e.g. hormones and contraceptives. The empty non-biodegradable implant has to be removed.

Intramuscular (IM)

Aqueous solution of the drug is injected into one of the large skeletal muscles—deltoid, triceps, gluteus or rectus femoris. Absorption into the plasma occurs by simple diffusion. Larger molecules enter through the lymphatic channels. As the muscles are vascular, absorption is rapid and quite uniform. Drugs are absorbed faster from the deltoid region than gluteal region especially in women. The volume of injection should not exceed 10 ml. For infants, rectus femoris is used instead of gluteus because gluteus is not well-developed till the child starts walking. If the drug is injected as oily solution or suspension, absorption is slow and steady and can have prolonged effect. Soluble substances, mild irritants, depot preparations, suspensions and colloids can be injected by this route.

Advantages

- Intramuscular route is reliable.
- Absorption is rapid.

Disadvantages

- Intramuscular injection may be painful
- May even result in an abscess. Local infection and tissue necrosis are possible.
- Nerve injury should be avoided—irritant solutions can damage the nerve, if injected near a nerve.
- In case of some drugs, absorption by IM route is slower than oral, e.g. diazepam, phenytoin.
- For some drugs, IM route should be avoided, e.g. heparin, calcium gluconate, diazepam, and tetracycline.

Intravenous (IV)

Here, the drug is injected into one of the superficial veins so that it directly reaches the circulation and is immediately available for action. Drugs can be given IV as:

1. *A bolus:* Where an initial large dose (loading dose) is given, e.g. heparin. The drug is dissolved in a suitable amount of the vehicle and injected slowly.
2. *Slow injection*—over 15–20 minutes, e.g. aminophylline.
3. *Slow infusion*—when constant plasma concentrations are required, e.g. oxytocin in labour or when large volumes have to be given, e.g. dextrose, saline. Generally, about one litre of solution is infused over 3 to 4 hours. However, the patient's condition and the drug factors like the onset and duration of action of the drug dictate the rate of infusion.

Advantages

- Most useful route in emergencies as the drug is immediately available for action.
- Provides predictable blood concentrations with 100% bioavailability.
- Large volumes of solutions can be given.
- Irritants can be given by this route as they get quickly diluted in blood.
- Rapid dose adjustments are possible—if unwanted effects occur, infusion can be stopped; if higher levels are required, infusion rate can be increased—specially for short-acting drugs.

Disadvantages

- Once injected, the drug cannot be withdrawn.
- Irritation of the veins may cause thrombophlebitis.
- Extravasation of some drugs may cause severe irritation and sloughing.
- Only aqueous solutions can be given IV but not suspensions, oily solutions and depot preparations.
- Self-medication is difficult.
- Risk of embolism—though rare.

Intraperitoneal

Peritoneum offers a large surface area for absorption. Fluids are injected intraperitoneally in infants. This route is also used for peritoneal dialysis.

Other Injections

Intrathecal: Drugs can be injected into the subarachnoid space for action on the CNS, e.g. spinal anaesthetics. Some antibiotics and corticosteroids are also injected by this route to produce high local concentrations. Strict aseptic precautions are a must.

Drugs are also given extradurally. Morphine can be given epidurally to produce analgesia. Direct intraventricular administration of drugs may be employed in brain tumors.

Intra-articular: Drugs are injected directly into a joint for the treatment of arthritis and other diseases of the joints, e.g. in rheumatoid

arthritis, hydrocortisone is injected into the affected joint. Strict aseptic precautions are required.

Intra-arterial: Intravenous and intra-arterial are intravascular routes. In intra-arterial route, the drug is injected directly into the arteries. It is used only in the treatment of:

1. Peripheral vascular diseases
2. Local malignancies
3. Diagnostic studies like angiograms.

Intramedullary: Injection into a bone marrow—now rarely used.

2. Inhalation

Lungs offer a large surface area for absorption of drugs. Volatile liquids and gases are given by inhalation, e.g. general anaesthetics. In addition, drugs can be administered as solid particles, i.e. solutions of drugs can be atomised and the fine droplets are inhaled as aerosol, e.g. salbutamol. These inhaled drugs and vapours may act locally on the pulmonary epithelium and mucous membranes of the respiratory tract or may also be absorbed through these membranes. The drug delivery by this route is influenced by the particle size and the breathing pattern. Drugs for inhalation are available as metered dose inhalers (MDI), dry powder inhalers (DPI) and nebulizers. In a metered dose inhaler, a solution containing multiple doses of particles of the drug, along with a propellant is stored under high pressure in a container. When the inhaler is activated, a fixed amount of the drug jets out of an orifice as a mist. In a dry powder inhaler, the drug is stored in a dry powder form. Nebulizers have the advantages that they do not require a propellant and the drug is delivered as small droplets which are breathed into the lungs.

Advantages

- Almost instantaneous absorption of the drug is achieved because of:
  - The large surface area of the lungs
  - Thin alveolar membrane
  - High vascularity
- In pulmonary diseases, inhalation serves almost as a local route as the drug is delivered at the desired site making it more effective and less harmful.
- Because the drug is directly delivered, smaller dose is needed and, therefore, toxicity is much less.
- Hepatic first pass metabolism is avoided.
- Blood levels of volatile anaesthetics can be conveniently controlled as their absorption and excretion through the lungs are governed by the laws of gases.

Disadvantages

- Irritant gases may enhance pulmonary secretion—should be avoided.
- Drug particles may induce cough, e.g. cromolyn sodium.

This is an important route of entry of certain drugs of abuse.

3. Transdermal

Highly lipid-soluble drugs can be applied over the skin for slow and prolonged absorption, e.g. nitroglycerine ointment in angina pectoris. Adhesive units, inunction, iontophoresis and jet injection are some forms of transdermal drug delivery.

***Adhesive units*:** Transdermal adhesive units (transdermal therapeutic systems) are adhesive patches (Fig. 1.2) of different sizes and shapes made to suit the area of application. The drug is held in a reservoir between an outer polymer layer and a porous membrane. The under surface of the membrane is smeared with an adhesive to hold on to the area of application. The drug slowly diffuses through the membrane and percutaneous absorption takes place. The rate of absorption is constant and predictable. Highly potent drugs (because small quantity is sufficient) and short-acting drugs (because

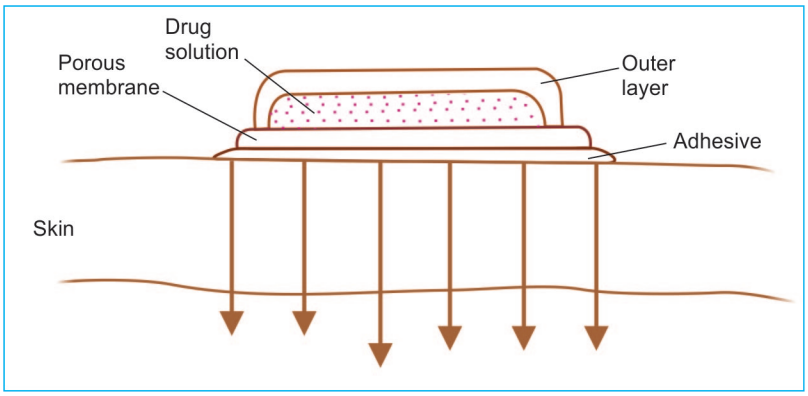


Fig. 1.2: Transdermal adhesive unit

effect terminates quickly after the system is removed) are suitable for use in such systems.

Sites of application depend on the indication—they may be applied over the chest, abdomen, upper arm, back or mastoid region; testosterone patch is applied over the scrotum.

For examples: Hyoscine, nitroglycerin, testosterone, oestrogen, nicotine and fentanyl transdermal patches (Table 1.2).

Advantages

- Duration of action is prolonged
- Provides constant plasma drug levels
- Patient compliance is good.

Disadvantages

- Large doses of the drug cannot be loaded into the system
- Can cause irritation to the skin
- Expensive.

Inunction: The route where a drug rubbed into the skin gets absorbed to produce systemic effects is called inunction.

Iontophoresis: Since flow of electricity enhances the permeability of the skin, in this procedure, galvanic current is used for bringing about penetration of lipid-insoluble drugs into the deeper tissues where their action is required, e.g. salicylates. Fluoride iontophoresis is used in the treatment of dental hypersensitivity.

Jet injection: As absorption of the drug occurs across the layers of the skin, dermojet may also be considered as a form of transdermal drug administration.

Table 1.2: Transdermal therapeutic system—some examples

Drug	*Site*	*Indication*
Nitroglycerin	Chest	Angina pectoris
Scopolamine	Mastoid region	Travelling sickness
Estrogen	Waist	Post-menopausal syndrome
Nicotine	Forearm/arm	To stop smoking
Testosterone	Scrotum, back, thigh	Deficiency
Fentanyl	Upper arm/back	Analgesic

LOCAL/TOPICAL APPLICATION

Drugs may be applied on the skin for local action as ointment, cream, gel, powder, paste, etc. Drugs may also be applied on the mucous membrane as in the eyes, conjunctiva, ears and nose as ointment, drops and sprays.

***Nasal*:** Drugs can be administered through nasal route either for systemic absorption or for local effects.

For example, for systemic absorption, oxytocin spray is used.

For local effect—decongestant nasal drops, e.g. oxymetazoline; budesonide nasal spray for allergic rhinitis.

Many drugs are administered as **suppository** for rectum, **bougie** for urethra and **pessary** and douche for vagina. Pessaries are oval-shaped tablets to be placed in the vagina to provide high local concentrations of the drug at the site, e.g. antifungal pessaries in vaginal candidiasis.

Douche is an aqueous solution used for rinsing a body cavity. Though the word 'douche' is generally used for vaginal solutions, it can also be used for solutions meant for bladder or the rectum.

Mnemonic for advantages and disadvantages of prodrugs (*see* page 7).

TATA Safari for Long Drive

T—↑ Tolerability
A—↑ Availability
T—Targeting possible
A—↓ ADR
S—Stability better
L—in Liver disease—not activated
D—↑ Duration of action

[1–5] From Medical Council of India, *Competency based Undergraduate Curriculum for the Indian Medical Graduate*, 2018;1:136–144.

CHAPTER 2

Pharmacokinetics

Competency achievement: The student should be able to:
PH 1.4 Describe absorption, distribution, metabolism and excretion of drugs.[1]

Pharmacokinetics is the study of the absorption, distribution, metabolism and excretion of drugs, i.e. the movement of the drugs into, within and out of the body. For a drug to produce its specific response, it should be present in adequate concentrations at the site of action. This depends on various factors apart from the dose. Once the drug is administered, it is absorbed, i.e. enters the blood, is distributed to different parts of the body, reaches the site of action, is metabolised and excreted (Fig. 2.1). All these processes involve passage of the drug molecules across various barriers—like the intestinal epithelium, cell membrane, renal filtering membrane, capillary barrier and so on. To cross these barriers, the drug has to cross

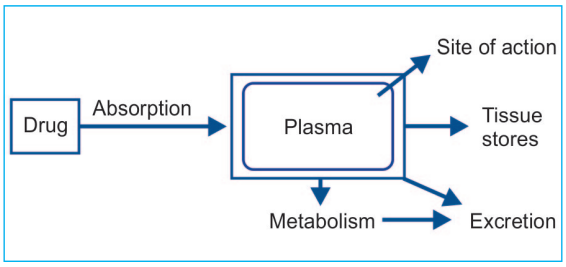


Fig. 2.1: Schematic representation of movement of drug in the body

the cell membrane or pass in-between the epithelial or endothelial cells.

The cell membrane/biological membrane is made up of two layers of phospholipids with intermingled protein molecules (Fig. 2.2). All lipid-soluble substances get dissolved in the cell membrane and readily permeate into the cells.

The junctions between adjacent epithelial or endothelial cells have pores through which

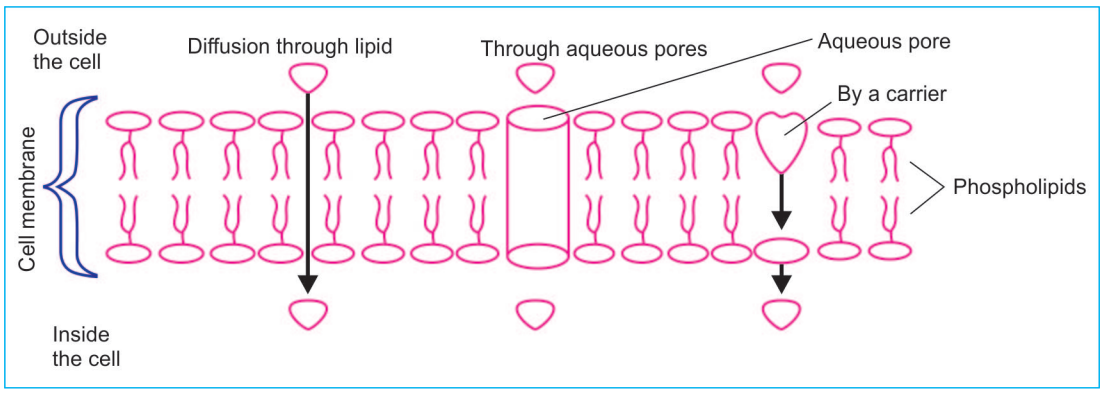


Fig. 2.2: Movement of drugs across biological membrane

small water-soluble molecules can pass. Movement of some specific substances is regulated by special carrier proteins. The passage of drugs across biological membranes or drug permeation involves processes like passive (filtration, diffusion) and active transports.

TRANSPORT OF DRUGS ACROSS BIOLOGICAL MEMBRANES

1. Passive transfer
   - Simple diffusion
   - Filtration
2. Carrier-mediated transport
   - Active transport
   - Facilitated diffusion
3. Endocytosis and exocytosis

Passive Transfer

The drug moves across a membrane without any need for energy.

Simple Diffusion

Simple diffusion is the transfer of a drug across the membrane in the direction of its concentration gradient. The speed of diffusion depends on the degree of concentration gradient, lipid solubility and ionisation. Higher the concentration gradient, faster is the diffusion across the membrane. Lipid-soluble, unionized drugs are rapidly transferred across membranes by simple diffusion—after dissolving in the lipids of the cell membrane (also called lipid diffusion). Most drugs follow simple diffusion.

Filtration

Filtration is the passage of drugs through aqueous pores in the membrane. Water-soluble drugs with molecular size (mol. wt. <100) smaller than the diameter of the pores (7Å) cross the biological membranes by filtration or aqueous diffusion. The movement is along the concentration gradient, e.g. urea.

The capillaries in certain tissues, like the brain and testes, lack the aqueous pores and may also contain efflux pumps. Thus many drugs do not reach them and are called **'sanctuary sites'**.

Carrier-mediated Transport

Transport of certain substances, which cannot move by diffusion, is aided by specific carriers.

Active Transport

Active transport is the transfer of drugs against a concentration gradient and needs energy. It is carried by a specific carrier protein. Only drugs related to natural metabolites are transported by this process, e.g. levodopa, iron, sugars and amino acids. The compound binds to a specific carrier on one side of the membrane and moves across the cell. At the other side of the cell, the complex dissociates and the carrier moves back to transport another molecule. Other substances competing for the same mechanism for transport may interfere with drug movement because this process is saturable, e.g. when penicillin and probenecid are administered together, the duration of action of penicillin is prolonged because both of them compete for renal tubular secretion.

Facilitated Diffusion

Facilitated diffusion is a unique form of carrier transport which differs from active transport in that it is not energy dependent and the movement occurs in the direction of the concentration gradient. The carrier facilitates diffusion and is highly specific for the substance, e.g. uptake of glucose by cells, vitamin B_{12} from intestines.

Endocytosis and Exocytosis

Endocytosis is the process where small droplets are engulfed by the cell membrane and carried into the cell as a vesicle. The vesicular membrane is then broken down to

release the substances. Some proteins and vitamin B_{12} with the help of intrinsic factor are taken up by this process (like pinocytosis in amoeba). This process is currently being tried for delivery of some anticancer drugs to the tissues. The reverse process—exocytosis is responsible for secretion of many substances from cells, e.g. neurotransmitters stored in nerve endings.

ABSORPTION

Absorption is defined as the passage of the drug from the site of administration into the circulation. For a drug to reach its site of action, it must pass through various membranes depending on the route of administration. Absorption occurs by one of the processes described above, i.e. passive diffusion or carrier-mediated transport. Thus except for intravenous route, the drug needs to be absorbed from all other routes of administration. The rate and extent of absorption varies with the route of administration.

Absorption from the Gut

Medication taken orally may be absorbed from any part of the gut. Highly lipid-soluble drugs may be absorbed from the buccal cavity from where it directly enters the systemic circulation. Acidic drugs are absorbed from the stomach, while basic drugs get ionised in the stomach and are not absorbed from the stomach (*see* below).

Intestines have a large surface area and most drugs are absorbed from the proximal part of the jejunum. Basic drugs are absorbed from the intestines because of the favourable pH. Various factors, like intestinal motility and pH, influence absorption from the gut. Absorption from the large intestine is negligible.

It has now been found that certain drugs may be transported out from the cells of the intestinal wall back into the gut lumen. This is done with a reverse transporter or efflux transporter P-glycoprotein.

Factors Influencing Drug Absorption

Several factors influence the rate and extent of absorption of a drug given orally (Fig. 2.3).

A. *Pharmaceutical factors*

1. **Disintegration and dissolution time:** The drug taken orally should break up into individual particles (disintegrate) to be absorbed. It then has to dissolve in the gastrointestinal fluids and the rate at which it dissolves influences absorption. In case of drugs given subcutaneously or intramuscularly, the drug molecules have to dissolve in the tissue fluids. Liquids are absorbed faster than solids. Delay in disintegration and dissolution as with poorly water-soluble drugs like aspirin, results in delayed absorption.
2. **Formulation:** Pharmaceutical preparations are formulated to produce desired absorption. Inert substances used with drugs as diluents like starch and lactose may sometimes interfere with absorption.
3. **Particle size:** Small particle size is important for better absorption of drugs. Drugs like corticosteroids, griseofulvin, digoxin, aspirin and tolbutamide are better absorbed when given as small particles. On the other hand, when a drug has to act on the gut and its absorption is not desired, then particle size should be kept large, e.g. anthelmintics like bephenium hydroxynaphthoate.

B. *Drug factors*

4. **Lipid solubility:** Lipid-soluble drugs are absorbed faster and better by dissolving in the phospholipids of the cell membrane.
5. **pH and ionisation:** Ionised drugs are poorly absorbed while unionised drugs are lipid-soluble and are well absorbed. Strong electrocytes are almost completely ionised at both acidic and alkaline pH. However, most drugs are weak electrolytes and exist in both ionised and unionised forms. The degree of ionisation depends on the pH of the medium. Thus acidic drugs remain unionised in acidic

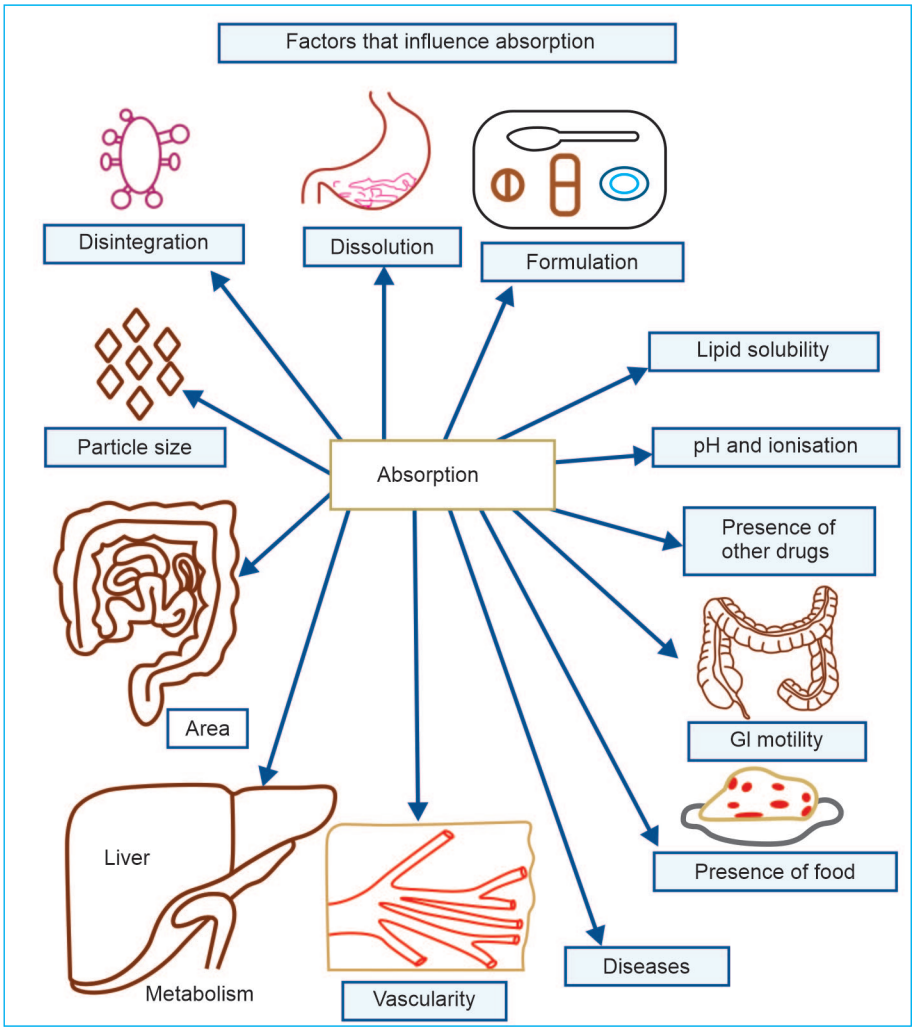


Fig. 2.3: Factors affecting absorption of drugs

medium of the stomach and are rapidly absorbed from the stomach, e.g. aspirin, barbiturates. Weakly acidic drugs form salts with bases and are available for use as sodium or potassium salts, e.g. phenobarbitone sodium, potassium penicillin-V. Weakly basic drugs form salts with acids and thus we have their hydrochlorides

and sulphates, e.g. ephedrine hydrochloride, atropine sulphate. Basic drugs are unionised when they reach the alkaline medium of the intestine from where they are rapidly absorbed, e.g. pethidine, ephedrine. Basic drugs given intravenously may diffuse from blood into the stomach because of acidic pH and may ionise quickly. This is known as 'ion trapping'. Strong acids and bases are highly ionised and, therefore, poorly absorbed, e.g. heparin, streptomycin.

The extent of trapping or the ratio of ionised to unionised form of a drug depends on the drug's acid dissociation constant (pKa) and the pH. The relationship between the dissociation constant of a drug (pKa) and the pH of the environment around it and the extent of its ionisation can be obtained by **Henderson-Hasselbalch equation**. From the equation, the ratio of the unionised form of the drug to its ionised form can be obtained.

Henderson-Hasselbalch equation

$$pKa = pH + \log \frac{\text{Concn. of nonionised acid}}{\text{Concn. of ionised acid}}$$

when pKa of the drug is equal to pH of the medium in which it is present, then the drug is 50% ionised and 50% unionised. In general, acidic drugs have low pKa (2.5–6), while basic drugs have higher pKa (8–10).

C. *Biological factors*

6. **Area and vascularity of the absorbing surface:** The larger the area of the absorbing surface and more the vascularity—better is the absorption. Thus most drugs are absorbed from the small intestine.

7. **Gastrointestinal motility**
   - Gastric emptying time—if gastric emptying is faster, the passage of the drug to the intestines is quicker and hence absorption is faster.
   - Intestinal motility—when highly increased as in diarrhoeas, drug absorption is reduced.

8. **Presence of food** delays gastric emptying, dilutes the drug and delays absorption. Drugs may form complexes with food constituents and such complexes are poorly absorbed, e.g. tetracyclines chelate calcium present in the food—hence their bioavailability is decreased. Moreover, certain drugs like ampicillin, roxithromycin and rifampicin are well absorbed only on empty stomach.

9. **Diseases** of the gut like malabsorption and achlorhydria result in reduced absorption of drugs. Particularly acidic drugs are poorly absorbed in presence of achlorhydria. In the absence of intrinsic factor, vitamin B_{12} is not absorbed in pernicious anemia.

10. **First pass metabolism:** Some drugs may be degraded in the GI tract, e.g. nitroglycerine, insulin (*see* below) before reaching the circulation.

First pass metabolism (Key Box 2.1) is the metabolism of a drug during its passage from the site of absorption to the systemic circulation. It is also called **presystemic metabolism** or **first pass effect** and is an important feature of oral route of administration. Such drugs should be given in higher doses or by

Key Box 2.1: First pass metabolism

- First pass metabolism is the metabolism of a drug during its first passage through the gut wall and liver to the systemic circulation
- Reduces bioavailability
- Extent of metabolism depends on the drug and individuals
- *Examples:* Morphine, chlorpromazine, nitroglycerin, verapamil, testosterone, insulin, lignocaine, salbutamol
- Measures to compensate first pass effect
  - Dose has to be increased for some drugs like propranolol
  - Route has to be changed for some others like hydrocortisone, insulin.

alternative routes. Drugs given orally may be metabolised in the gut wall and in the liver before reaching the systemic circulation. The extent of first pass metabolism differs from drug to drug and among individuals from partial to total inactivation.

Clinical Significance

When it is partial, it can be compensated by giving higher dose of the particular drug, e.g. nitroglycerine, propranolol, salbutamol. For drugs that undergo complete first pass metabolism, the route of administration has to be changed, e.g. isoprenaline, hydrocortisone, insulin.

Bioavailability of many drugs is increased in patients with liver disease due to reduction in hepatic metabolism.

Extent of first pass metabolism may vary between individuals and fixing the dose may be a problem.

Absorption from Parenteral Routes

On **intravenous administration,** the drug directly reaches the circulation (Fig. 2.4). On **intramuscular injection,** the drug is deposited in the muscles and the drug molecules should dissolve in the tissue fluids and then be absorbed. Since muscles have a rich blood supply, absorption is fast. Drug molecules diffuse through the capillary membrane and reach the circulation. Lipid-soluble drugs are absorbed faster.

Absorption from **subcutaneous administration** is slower but rate of absorption is somewhat steady. Hyaluronidase increases rate of absorption.

Inhaled drugs are rapidly absorbed from the pulmonary epithelium particularly the lipid-soluble ones.

On topical application, highly lipid-soluble drugs are absorbed from the intact skin, e.g. nitroglycerine; but absorption is relatively slow because of the multiple layers of closely-packed cells in the epidermis. Most drugs are readily absorbed from the mucous membranes.

BIOAVAILABILITY

Definition: Bioavailability is the fraction (F) of the administered drug that reaches the

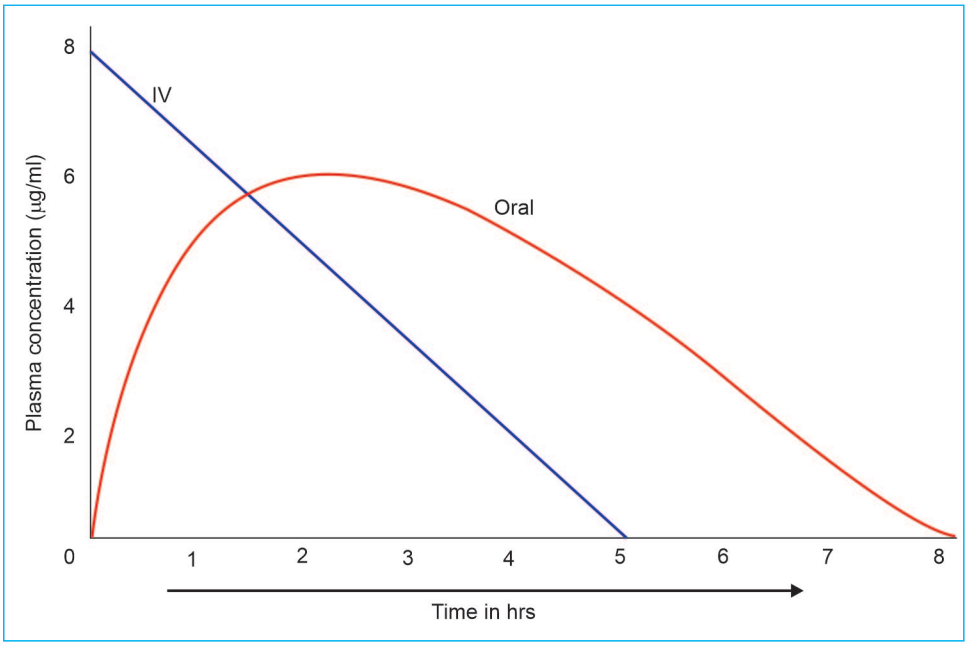


Fig. 2.4: Plasma concentration–time curve of a drug following a single oral and IV dose

systemic circulation in unchanged form following administration by any route.

Thus, when a drug is given intravenously, the bioavailability is 100%. On IM/SC injection and sublingual administration, drugs are almost completely absorbed (bioavailability >75%) while by oral route, bioavailability may be low due to incomplete absorption and first pass metabolism, e.g. bioavailability of chlortetracycline is 30%, carbamazepine—70%, chloroquine—80%, minocycline and diazepam almost 100%.

Transdermal preparations are absorbed systemically and may have 80–100% bioavailability while for rectal administration it may be 30% to almost 100%. Large bioavailability variations of a drug, particularly when it is unpredictable, can result in toxicity or therapeutic failure as in case of halofantrine.

Factors that influence bioavailability: In fact, all the ten factors which influence the absorption of a drug including the pharmaceutical factors, drug factors and biological factors also alter bioavailability. Drugs which undergo extensive first pass metabolism have a low bioavailability. In general, unionised drugs with good lipid solubility and of small particle size have good bioavailability since they are well absorbed.

Determining bioavailability: The drug is injected intravenously and its plasma concentration is measured at one hourly intervals. The plasma concentration is plotted against time on a graph paper. Similarly plasma concentration–time graph is also obtained, after oral administration of the same dose of the drug. Once these curves are obtained, the area under the curve (AUC) is measured (Fig. 2.5). From such a curve, we know the maximum concentration attained following absorption (E_{max}), the time taken for it (T_{max}) and the extent of absorption from area under the curve.

Bioavailability is calculated by the formula:

$$\text{Bioavailability (F)} = \frac{\text{AUC (oral)} \times 100}{\text{AUC (IV)}}$$

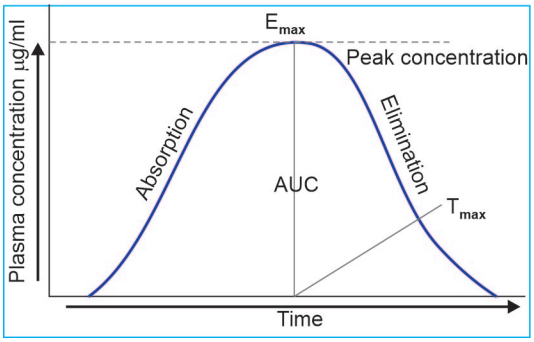


Fig. 2.5: Graph showing peak plasma concentration (E_{max}), time to peak plasma concentration (T_{max}) and area under the curve (AUC) which are the parameters of bioavailability

EQUIVALENCE

1. Chemical equivalence: If two-dosage forms of a drug contain the same amount of the drug, they are said to be chemically equivalent.

2. Bioequivalence: If two formulations of a drug have the same bioavailability, they are bioequivalent.

Comparison of bioavailability of different formulations of the same drug is the study of bioequivalence. If two drug formulations have the same bioavailability and rate of absorption, they are bioequivalent. Often oral formulations containing the same amount of a drug (pharmaceutically equivalent) from different manufacturers may result in different plasma concentrations, or may differ in the rate of absorption, i.e. there is no bioequivalence among them (Fig. 2.6). Such differences occur

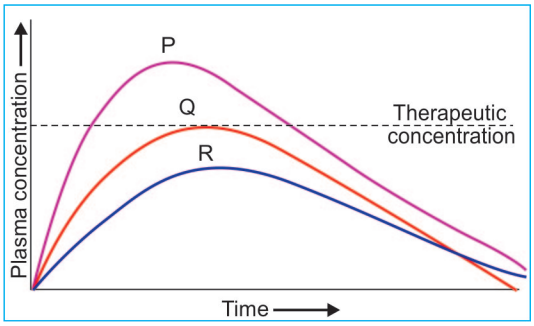


Fig. 2.6: Study of bioequivalence—three different oral formulations—P, Q and R of the same drug yield different bioavailability values. The area under each curve gives the bioavailability of the respective formulation

with poorly soluble, slowly absorbed drugs, mainly due to differences in the rate of disintegration and dissolution. Variation in bioavailability (non-equivalence) can result in toxicity or therapeutic failure of drugs that have low safety margin like digoxin and drugs that need precise dose adjustments like anti-coagulants and corticosteroids. For such drugs, in a given patient, the preparations from a single manufacturer should be used.

3. Therapeutic equivalence: If two drugs produce the same therapeutic response, they are said to be therapeutically equivalent. For example, if drug A and drug B can produce the same degree of diuresis, they are said to be therapeutically equivalent.

DISTRIBUTION

After a drug reaches the systemic circulation, it gets distributed to other tissues. It should cross several barriers before reaching the site of action. Like absorption, distribution also involves the same processes, i.e. filtration, diffusion and specialized transport. Various factors determine the rate and extent of distribution, viz. lipid solubility, ionization, blood flow and binding to plasma proteins and cellular proteins. Unionized lipid-soluble drugs are widely distributed throughout the body.

Plasma Protein Binding

On reaching the circulation, most drugs bind to plasma proteins; acidic drugs bind mainly albumin and basic drugs to alpha-acid glycoprotein. The free or unbound fraction of the drug is the only form available for action, metabolism and excretion while the protein bound form serves as a reservoir (Fig. 2.7). The extent of protein binding varies with each drug, e.g. warfarin is 99% and morphine is 35% protein bound while binding of ethosuximide and lithium is 0%, i.e. they are totally free (Table 2.1).

Some drugs also bind to tissue proteins (*see* as follows) and specific carrier proteins (e.g. corticosteroids to transcortin, iron to ferritin).

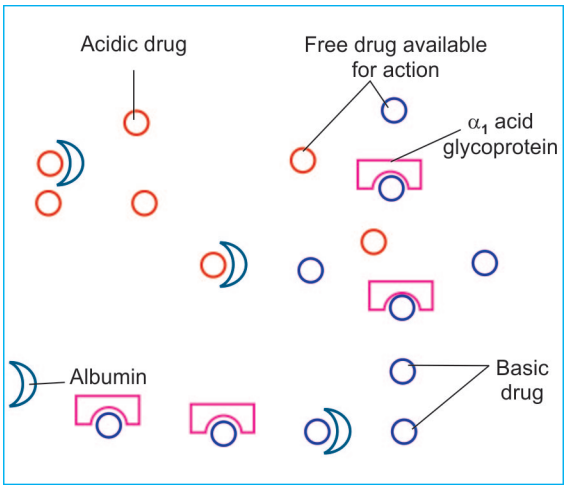


Fig. 2.7: Plasma protein binding

Table 2.1: Some highly protein bound drugs

Warfarin	Tolbutamide	Phenytoin
Frusemide	Clofibrate	Sulfonamides
Diazepam	Salicylates	Phenylbutazone
Indomethacin		

Some drugs not bound to plasma proteins

Isoniazid	Lisinopril
Lithium	Ethosuximide
Metformin	

Clinical Significance of Plasma Protein Binding

1. Only free fraction is available for action, metabolism and excretion. When the free drug levels in the plasma fall, bound drug is released. Thus protein binding may delay the drug reaching the site of action.
2. Protein binding serves as a store (reservoir) of the drug and the drug is released when free drug levels fall.
3. Protein binding prolongs the half-life and thereby the duration of action of the drug because the bound form is protected from metabolism and excretion. Bound form is not filtered at the glomerulus and the excretion is therefore delayed. Highly protein bound drugs are generally long-acting.

4. Many drugs may compete for the same binding sites. Thus one drug which has higher affinity for the binding site may displace another from the binding sites and result in displacement interactions, e.g. warfarin is 99% bound to albumin (i.e. free fraction is 1%). If another drug, like indomethacin, reduces its binding to 95%, the free form then becomes 5% which means, there is a 5-fold increase in free warfarin levels which could result in toxicity. Fortunately, the body largely compensates by enhancing metabolism and excretion.
5. Protein binding sites may get saturated with repeated administration of the drug and thereafter more and more drug will remain in the free form.
6. Chronic renal failure and chronic liver disease result in hypoalbuminaemia with reduced protein binding of drugs leading to raised levels of free drug. The normal plasma albumin concentration is 0.6 mm/litre. Highly protein bound drugs should be carefully used in such patients because even therapeutic doses of such drugs can result in toxicity and may require dose reduction.
7. In pregnancy, there is an increase in thyroxine binding protein levels resulting in reduced free thyroxine levels.
8. In acute inflammatory states, alpha 1 acid glycoprotein levels may rise resulting in more extensive binding and thereby lower free drug levels—hence, higher doses may be needed.

Tissue Binding

Some drugs get bound to certain tissue constituents because of special affinity for them as given in Key Box 2.2.

Tissue binding delays elimination and thus prolongs duration of action of the drug. For example, lipid-soluble drugs are bound to adipose tissue. Tissue binding also serves as a **reservoir** of the drug.

Key Box 2.2: Special affinity of drugs for tissues

Tissue	*Binding drugs*
Adipose tissue	Thiopentone sodium, benzodiazepines
Muscles	Emetine
Bone	Tetracyclines, lead
Retina	Chloroquine
Thyroid	Iodine

Redistribution

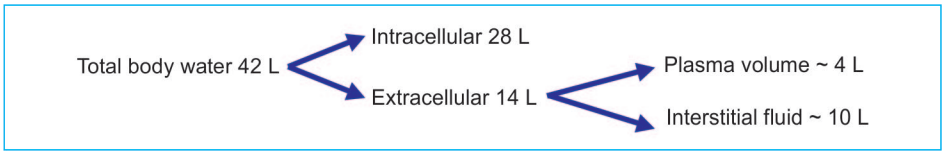
When some highly lipid-soluble drugs are given intravenously or by inhalation, they get rapidly distributed into highly perfused tissues like the brain, heart and kidney. But soon they get redistributed into less vascular tissues like the muscle and fat resulting in termination of the action of these drugs. The best example is the intravenous anaesthetic thiopental sodium which induces anaesthesia in 10–20 seconds but the effect ceases in 5–15 minutes due to redistribution.

Blood–Brain Barrier (BBB)

The endothelial cells of the brain capillaries lack intercellular pores and instead have tight junctions. Moreover, glial cells envelope the capillaries and together these form the BBB. Drugs have to pass through the cells to cross the barrier (Key Box 2.3). Only lipid-soluble, unionised drugs can cross this BBB. During inflammation of the meninges, the barrier becomes more permeable to drugs, e.g. penicillin readily penetrates during meningitis. The barrier is weak at some areas like CTZ, posterior pituitary and parts of hypothalamus and allows some compounds to diffuse. Since the pH of CSF is 7.35, weakly basic drugs concentrate in it more than the acidic drugs.

Key Box 2.3: Sites which are 'difficult to enter' for drugs

- CSF
- Lymph
- Ocular fluids
- Pleural fluids
- Synovial fluid



Placental Barrier

Lipid-soluble, unionised drugs readily cross the placenta while lipid-insoluble drugs cross to a much lesser extent. Thus drugs taken by the mother can cause several unwanted effects in the foetus. Lipid-soluble drugs with molecular weight of about 200–500 can easily cross the placenta while those with large molecular size (mol.wt >1000) can hardly cross the placenta. These require transporters for crossing the placenta.

VOLUME OF DISTRIBUTION (V)

For the purpose of pharmacokinetic studies, body can be considered as a single compartment into which drugs are distributed uniformly. Each drug actually follows its own pattern of distribution from plasma to other body fluids and tissues.

Apparent Volume of Distribution

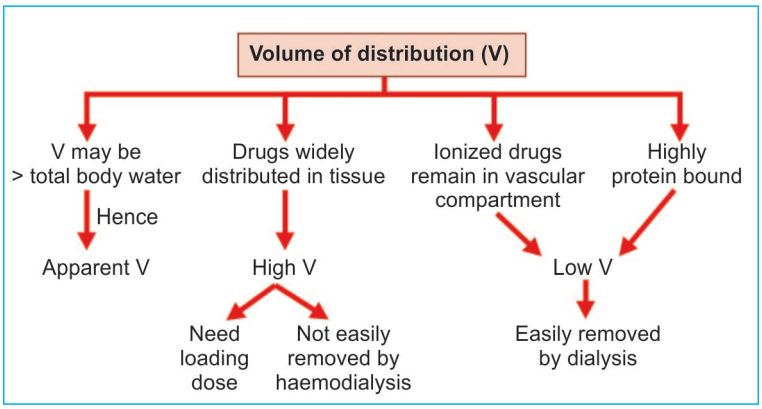
Apparent volume of distribution is a hypothetical concept. This is defined as the volume necessary to accommodate the entire amount of the drug administered, if the concentration throughout the body is equal to that in plasma. It can also be defined as the volume in which the drug can be evenly distributed, if the concentration attained was equal to that in plasma. It is called 'apparent' as the volume here is 'apparently' needed to hold the drug and the uniform distribution of the drug is presumed. It relates the amount of the drug in the body to the concentration (C) of the drug in plasma. The volume so calculated can be more than the total body water and is therefore called the 'apparent' volume of distribution. It is calculated as:

$$V = \frac{\text{Amount of drug in the body}}{\text{Plasma concentration (C)}}$$

e.g. if the dose of a drug given is 500 mg and it attains a uniform concentration of 10 mg/litre of plasma in the body, its V = 50 litres.

Important facts about V are:

- If a drug is retained mostly in the plasma, its V is small (e.g. aspirin, aminoglycosides) while if it is distributed widely in tissues, then its V is large (e.g. pethidine). V may vary with changes in tissue permeability and protein binding as seen in some diseases.
- Highly lipid-soluble drugs that get sequestered in the adipocytes have a large V (e.g. chloroquine ~13000 L). Drugs with



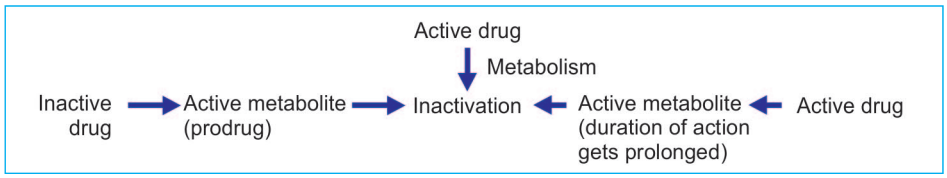


Fig. 2.8: Biotransformation

large *V* need to be given as loading dose (e.g. chloroquine) to attain therapeutic concentration. Drugs extensively bound to plasma proteins have a low *V* (~3L), e.g. phenylbutazone.

- Ionised drugs have a low 'V' as they remain in the vascular compartment. Low *V* drugs may have a larger *V* in presence of oedema or ascites due to increased ECF volume.
- In conditions like CCF, uraemia and cirrhosis, *V* could change since reduced perfusion of tissues would lead to reduced *V*.
- The knowledge of *V* of drugs is clinically important in the treatment of poisoning. Drugs with large *V* like pethidine are not easily removed by haemodialysis because such drugs are widely distributed in the body.

Factors affecting *V*—plasma protein binding, pKa of the drug, special affinity for the tissues and diseases like cirrhosis and CCF.

BIOTRANSFORMATION (METABOLISM)

Biotransformation is the process of biochemical alteration of the drug in the body. Body treats most drugs as foreign substances (called xenobiotics) and tries to inactivate and eliminate them by various biochemical reactions. These processes convert the non-polar, lipid soluble drugs into more polar, water-soluble compounds so that they are easily excreted through the kidneys and not reabsorbed. Some drugs may be excreted largely unchanged in the urine, e.g. frusemide, atenolol (Figs 2.8, 2.9 and Table 2.2)

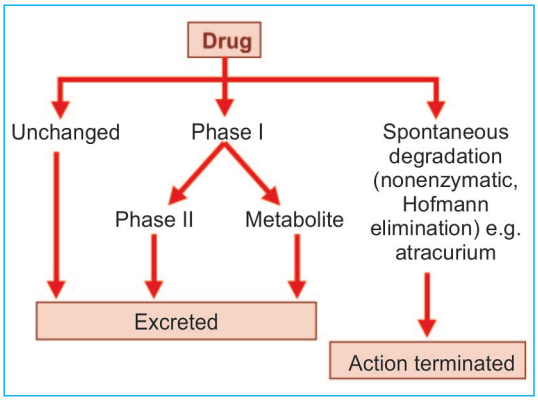


Fig. 2.9: Phases in metabolism of drugs. A drug may be excreted as phase I metabolite or as phase II metabolite. Some drugs may be excreted as such

Table 2.2: Important drug biotransformation reactions

Reactions	*Examples of drugs*
Phase I reactions	
Oxidation	Phenytoin, diazepam, ibuprofen, amphetamine, chlorpromazine, dapsone
Reduction	Chloramphenicol, halothane
Hydrolysis	Pethidine, procaine, enalapril
Phase II reactions (conjugation reactions)	
Glucuronide conjugation	Chloramphenicol, morphine, diazepam, aspirin
Acetylation	Sulfonamides, isoniazid
Methylation	Adrenaline, noradrenaline, dopamine, histamine
Glutathione conjugation	Paracetamol
Sulphate conjugation	Paracetamol, steroids
Amino acid conjugation	Salicylic acid, benzoic acid

Site

The most important organ of biotransformation is the liver. Drugs are also metabolised though to a small extent by the kidney, gut mucosa, lungs, blood and skin.

Consequences of Biotransformation

Though biotransformation generally inactivates the drug, some drugs may be converted to metabolites which are also active or more active than the parent drug.

Biotransformation reactions may result in any or all of the following (Table 2.3)

1. **Inactivation**—Largely biotransformation inactivates the drug and most drugs are converted to inactive metabolites, e.g. phenytoin, paracetamol, phenobarbitone.
2. Formation of active metabolite—(active drug to active metabolite) biotransformation may convert the drug partly to metabolites which are also active or more active than the parent drug, e.g. diazepam to oxazepam; such generation of active metabolites prolongs the duration of action of the drug.
3. Activation of inactive drug—prodrug is an inactive drug which gets converted into an active drug in the body, e.g. Levodopa to dopamine
4. Formation of toxic metabolite—in case of some drugs, the active metabolite may be toxic. For example, paracetamol is converted to N-acetyl-p-benzoquinoneimine (NAPQI) which causes hepatotoxicity; cyclophosphamide is converted to acrolein which causes bladder toxicity.

Some drugs may be converted to epoxides which are short acting but highly reactive molecules. They bind to cells and tissues resulting in toxicity. Epoxide-induced liver damage is countered to a large extent by glutathione conjugation.

Enzymes in Biotransformation

The biotransformation reactions are catalysed by specific enzymes located either in the liver microsomes (microsomal enzymes) or in the cytoplasm and mitochondria of the liver cells and also in the plasma and other tissues (non-microsomal enzymes).

Microsomal enzymes are a mixed function oxidase system or mono-oxygenases and require nicotine adenine dinucleotide phosphate (NADPH) and oxygen. Microsomal enzymes cytochrome P450 (CYP) are important in the oxidation reduction reactions. There are several isoforms of the P450 enzymes. Several CYP gene families are known, of which the first three—CYP1, CYP2 and CYP3—are important groups. Some isozymes are CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP3A4 and are the most important enzymes involved in biotransformation in the liver. CYP3A4 alone is found to metabolise nearly 50% of the drugs degraded in the liver.

The chemical reactions of biotransformation can take place in two phases (Fig. 2.9):

1. Phase I (non-synthetic reactions)
2. Phase II (synthetic reactions).

Table 2.3: Consequences of biotransformation with examples

Active drug to inactive metabolite	*Active drug to active metabolite*	*Inactive drug to active metabolite (prodrug)*
Examples	Examples	Examples
• Phenobarbitone → hydroxy phenobarbitone • Phenytoin → hydroxyphenytoin	• Primidone ▸ Phenobarbitone • Digitoxin ▸ Digoxin • Diazepam ▸ Oxazepam • Allopurinol ▸ Alloxanthine	• Levodopa ▸ Dopamine • Prednisone ▸ Prednisolone • Enalapril ▸ Enalaprilat • Bacampicillin ▸ Ampicillin

Phase I Reactions

Phase I reactions convert the drug to a more polar metabolite by oxidation, reduction or hydrolysis.

1. Oxidation is the process of addition of oxygen (or a negatively charged radical) to a drug molecule or removal of hydrogen (or a positively charged radical) from a drug molecule. Oxidation reactions are the most important metabolizing reactions, mostly catalyzed by mono-oxygenases present in the liver (Table 2.4). They are carried on by a system which includes cytochrome P450, NADPH and molecular oxygen. There are several types of oxidation reactions like:

A. *Microsomal oxidation*

i. S-oxidation (sulfoxidation)
   Cimetidine → cimetidine sulfoxide
ii. N-oxidation
   Dapsone → hydroxylamine dapsone
ii. Dealkylation
   Imipramine → desmethylimipramine
   Codeine → morphine
iii. Hydroxylation
   Salicylic acid → gentisic acid
   Phenytoin → hydroxy phenytoin
iv. Deamination
   Amphetamine → Benzyl methyl ketone

B. *Non-microsomal oxidation*

Oxidation can also be catalysed by non-microsomal enzymes like monoamino oxidase, xanthine oxidase, alcohol dehydrogenase and aldehyde dehydrogenase.

Example: Ethyl alcohol → CO_2 + H_2O

2. Reduction may be catalysed by microsomal or non-microsomal enzymes. Microsomal reduction reactions include

i. Nitro reduction
   e.g. Chloramphenicol → Arylamine
ii. Keto reduction
   e.g. Cortisone → hydrocortisone

Disulfiram and nitrites are reduced by **non-microsomal enzymes** (Fig. 2.10).

3. Hydrolysis is the process where a drug molecule is 'split' by the addition of a molecule of water (both microsomal and non-

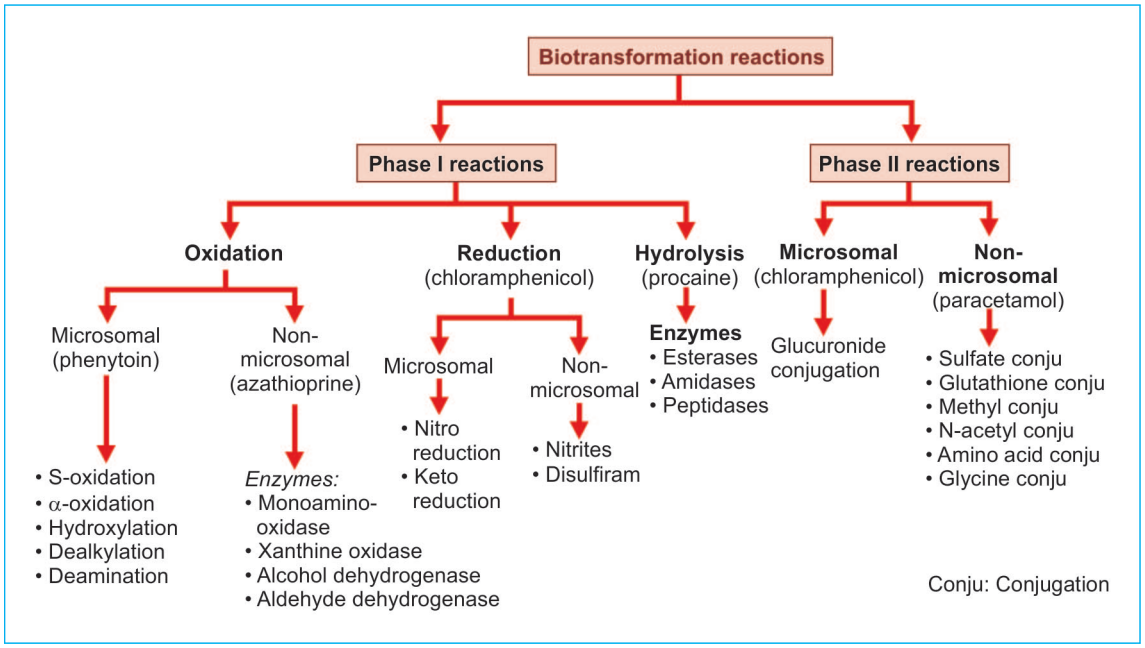


Fig. 2.10: Types of biotransformation reactions with examples

microsomal enzymes may be involved). Esterases, amidases and peptidases catalyze hydrolytic reactions are non-microsomal enzymes.

For example:

Acetylcholine + H_2O → Choline + Acetic acid

Other drugs like lignocaine, procaine, atropine, pethidine and neostigmine are metabolized by hydrolysis.

If the metabolite of phase I reaction is not sufficiently polar to be excreted, it undergoes phase II reactions.

Phase II Reactions

In phase II reactions, endogenous water-soluble substances like glucuronic acid, sulfuric acid, glutathione or an amino acid combine with the drug or its phase I metabolite to form a highly polar conjugate which is inactive and gets readily excreted by the kidneys. Large molecules are excreted through the bile. **Conjugation** results invariably in inactivation of the drug. Some products of conjugation are glucuronides, ethereal sulphates and amino acid conjugates.

Microsomal conjugation reaction

Glucuronide conjugation is the most common type of metabolic reaction. Endogenous substances like bilirubin and steroid hormones also undergo conjugation.

The drug or its phase I metabolite undergoes conjugation with uridine diphosphate glucuronic acid (UDPGA) followed by transfer of glucuronic acid to the drug. The reaction is catalysed by the enzyme UDP glucuronyl transferase and the drug—glucuronide conjugate formed is polar, inactive and can be readily excreted through the kidneys.

$$\text{Drug} + \text{UDPGA} \xrightarrow[\text{transferase}]{\text{Glucuronyl}} \text{Drug glucuronide} + \text{UDP}$$

$$\downarrow$$

$$\text{Excreted}$$

e.g.

Morphine + Glucuronic acid → Morphine glucuronide

The enzyme glucuronyl transferase is not adequately formed in the neonate. Hence bilirubin levels increase and result in **neonatal jaundice**. Grey baby syndrome—an adverse effect to high doses of chloramphenicol seen in neonates is also because of the lack of UDP glucuronyl transferase.

Several endogenous substances involved in conjugation are supplied by the diet. Hence nutrition is also important for conjugation and thereby detoxification of the drugs.

Non-microsomal conjugation reactions

i. **Acetylation (acetyl conjugation):** Drugs like sulfonamides and isoniazid undergo conjugation with acetylcoenzyme A. This acetylation is catalysed by N-acetyl-transferase found in the cytoplasm.

ii. **Methylation (methyl conjugation):** Catecholamines, like adrenaline and dopamine, undergo methyl conjugation or methylation catalyzed by the enzyme transmethylase. The methyl group is donated by methionine and cysteine. The following are other conjugation reactions.

iii. **Glutathione conjugation:** Though a minor pathway of metabolism, glutathione conjugation inactivates highly reactive intermediates formed during the metabolism of drugs like paracetamol. Many epoxides and drugs with nitrate groups undergo glutathione conjugation with the help of the enzyme glutathion-S-transferase.

iv. **Amino acid conjugation** is a minor pathway for metabolism of certain acidic drugs like aspirin, for example: Benzoic acid + glycine → Hippuric acid

v. **Sulfate conjugation** is catalyzed by sulfo-transferases, e.g steroids, chloram-phenicol, methyldopa. Sulfation can also result in the conversion of minoxidil, a prodrug into its active metabolite.

vi. **Glycine conjugation** though also a minor metabolic pathway, drugs like salicylates are conjugated with glycine.

Hofmann Elimination

Some drugs undergo a unique type of metabolism—they are metabolised by spontaneous degradation due to spontaneous molecular rearrangement in plasma and tissues, e.g. atracurium and cisatracurium—called Hofmann degradation which adds to their short action.

ENZYME INDUCTION

Microsomal enzymes are located in the microsomes that line the smooth endoplasmic reticulum of the liver cells. The **synthesis** of these microsomal enzymes, mainly cytochrome P450, can be enhanced by certain drugs and environmental pollutants. This is called **enzyme induction** and this process speeds up the biotransformation of the inducing drug itself and also other drugs metabolised by the same microsomal enzymes, e.g. phenobarbitone, rifampicin, alcohol, cigarette smoke, DDT (environmental pollutants), griseofulvin, carbamazepine, phenytoin and many antiretroviral drugs like nevirapine and efavirenz are enzyme inducers.

Enzyme induction may be selective for some particular enzymes (as with DDT) or may be nonselective as with phenobarbitone which could induce most microsomal enzymes. Enzyme induction may be blocked by drugs that inhibit protein synthesis. Enzymes are induced gradually and take about 1–2 weeks for peak effect and induction continues till the drug is administered. However, it is reversible and the enzyme levels return to initial levels in about 1–3 weeks. Enzyme induction can enhance drug metabolism by 2–4 times. However, it can also result in toxicity if the metabolite is toxic.

Clinical Relevance of Microsomal Enzyme Induction

1. *Drug interactions*
   a. ***Therapeutic failure:*** By speeding up metabolism, enzyme induction may reduce the duration of action of some other drugs which can result in therapeutic failure, e.g. failure of oral contraceptives in patients taking rifampicin.

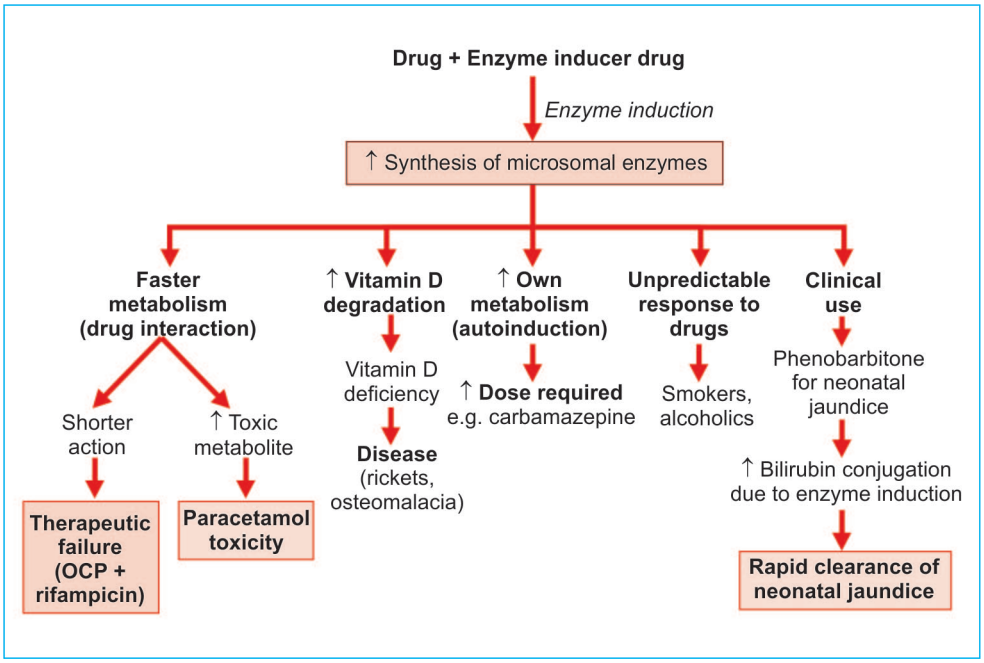


Fig. 2.11: Clinical significance of enzyme induction

b. ***Toxicity:*** Enzyme induction may result in toxicity due to production of higher amounts of the toxic intermediate metabolites, e.g. a patient undergoing treatment with rifampicin is likely to develop hepatotoxicity with paracetamol because a higher amount of the toxic intermediate metabolite of paracetamol is formed due to enzyme induction.

2. *Tolerance to drugs* may develop as in case of carbamazepine since it induces its own metabolism called **autoinduction**.
3. *Result in disease:* Antiepileptics enhance the breakdown of vitamin D resulting in osteomalacia on long-term administration.
4. *Variable response:* In chronic smokers and alcoholics, enzyme induction may result in failure to achieve the expected response to some drugs metabolised by the same enzymes.
5. *Therapeutic application of enzyme induction:* Neonates are deficient in both microsomal and non-microsomal enzymes. Hence their capacity to conjugate bilirubin is low which results in jaundice. Administration of phenobarbitone, an enzyme inducer, helps in rapid clearance of the jaundice in the neonates by enhancing bilirubin conjugation.

Enzyme Inhibition

Some drugs inhibit cytochrome P450 enzyme activity. Drugs like cimetidine bind to cytochrome P450 and competitively inhibit the metabolism of endogenous substances like testosterone and other drugs given concurrently. Enzyme inhibition by drugs is the basis of several drug interactions. Chloramphenicol, erythromycin, ketoconazole, cimetidine, ciprofloxacin and verapamil are some enzyme inhibitors. With some drugs, the binding of enzymes may be irreversible—leading to inactivation of the enzyme. Such substrates are called **suicide inhibitors**, e.g. selegiline, ticlopidine, clopidogrel and prophylthiouracil.

Many of the antiretroviral drugs used in AIDS are enzyme inhibitors.

Drugs could also inhibit other enzymes, i.e. **non-microsomal enzymes**. Such inhibition could be competitive or non-competitive inhibition.

Competitive enzyme inhibitors are structurally similar to the natural substrates and thereby compete for binding to the enzyme. This type of enzyme inhibition may be reversed by higher substrate concentration. For example, xanthine oxidase inhibition by allopurinol. However, if the binding takes place by covalent bonds, then it could be irreversible like organophosphates inhibiting acetylcholinesterase.

Competitive Inhibitors

Drugs	Enzyme inhibited
Captopril	Angiotensin converting enzyme
Allopurinol	Xanthine oxidase
Sulfonamide	Folic acid synthetase
Meclobemide	MAO-A
Neostigmine, organophosphates	Acetylcholinesterase

Non-competitive inhibition: Here there is no structural similarity and the inhibition is generally irreversible because such drugs prevent the formation of enzyme substrate complex by altering the structure of the enzyme. New enzymes need to be synthesized to resume activity. For example, statins inhibiting HMG-CoA reductase.

Non-competitive Inhibitors

Drugs	Enzymes inhibited
Disulfiram	Aldehyde dehydrogenase
Isocarboxazid	Monoamino-oxidase
Statins	HMG-CoA reductase
Digoxin	Na^+-K^+-ATPase
Sildenafil	Phosphodiesterase

Factors that Influence Biotransformation

- *Genetic variation* results in altered metabolism of drugs, e.g. succinylcholine is metabolised very slowly in people with defective pseudocholinesterase resulting in prolonged apnoea.
- *Environmental pollutants,* like cigarette smoke, cause enzyme induction.
- *Age:* At extremes of age, the activity of metabolic enzymes in the liver are low and hence there is increased risk of toxicity with drugs.
- *Diseases of the liver:* Markedly affect metabolism of drugs.

EXCRETION

Drugs are excreted from the body after being converted to water-soluble metabolites while some are directly eliminated without metabolism. The major organs of excretion are the kidneys, the intestine, the biliary system and the lungs. Drugs are also excreted in small amounts in the saliva, sweat and milk.

Renal Excretion

Kidney is the most important organ of drug excretion. The three processes involved in the elimination of drugs through kidneys are glomerular filtration, active tubular secretion and passive tubular reabsorption.

Glomerular Filtration

The rate of filtration through the glomerulus depends on GFR, concentration of free drug in the plasma and its molecular weight. Ionised drugs of low molecular weight (<10,000) are easily filtered through the glomerular membrane.

Active Tubular Secretion

Cells of the proximal tubules actively secrete acids and bases by two transport systems. Thus acids like penicillin, salicylic acid, probenecid, frusemide; bases like amphetamine and histamine are so excreted. Drugs may compete for the same transport system resulting in prolongation of action of each other, e.g. penicillin and probenecid.

Passive Tubular Reabsorption

Passive diffusion of drug molecules can occur in either direction in the renal tubules depending on the drug concentration, lipid solubility and pH. As highly lipid-soluble drugs are largely reabsorbed, their excretion is slow. Acidic drugs get ionised in alkaline urine and are easily excreted while bases are excreted faster in acidic urine. This property is useful in the treatment of poisoning. In poisoning with acidic drugs like salicylates and barbiturates, forced alkaline diuresis (diuretic + sodium bicarbonate + IV fluids) is employed to hasten drug excretion. Similarly, elimination of basic drugs, like quinine and amphetamine, is enhanced by forced acid diuresis.

Faecal and Biliary Excretion

Unabsorbed portions of the orally administered drugs are eliminated through the faeces. Liver transfers acids, bases and unionised molecules into bile by specific acid transport processes. Large water-soluble conjugates are excreted in the bile. Some drugs may get reabsorbed in the lower portion of the gut and are carried back to the liver. Such recycling is called enterohepatic circulation and it prolongs the duration of action of the drug; examples are chloramphenicol, tetracycline, oral contraceptives and erythromycin.

Pulmonary Excretion

The lungs are the main route of elimination for gases and volatile liquids, viz. general anaesthetics and alcohol. The drug is eliminated with the expired air and is dependent on the rate of respiration and the blood flow to the lungs. This also has legal implications in medicolegal practice as the breath analyser is used to measure alcohol levels in the expired air in vehicle drivers.

Other Routes of Excretion

Small amounts of some drugs are eliminated through the sweat and saliva. Excretion in saliva may result in a unique taste of some drugs like phenytoin, clarithromycin; metallic

Table 2.4: Example of drugs that could be toxic to the suckling infant when taken by the mother

Sulphasalazine	Doxepin
Theophylline	Amiodarone
Anticancer drugs	Primidone
Salicylates	Ethosuximide
Chloramphenicol	Phenobarbitone
Nalidixic acid	Phenothiazines

taste with metronidazole, metoclopramide and disulfiram. Drugs like iodide, rifampicin and heavy metals are excreted through sweat.

The excretion of drugs in the milk is in small amounts and is of no significance to the mother. However, for the suckling infant, it may be sometimes important especially because of the infant's immature metabolic and excretory mechanisms. Though most drugs can be taken by the mother without significant toxicity to the child, there are a few exceptions (Table 2.4).

CLINICAL PHARMACOKINETICS

The knowledge of pharmacokinetics is clinically useful for several purposes including selection and adjustment of the dosage regimen, and to obtain optimum effects from a drug. The three most important pharmacokinetic parameters are bioavailability (*see* page 23), volume of distribution (*see* page 27) and clearance.

Clearance (CL)

Clearance is the volume of plasma freed completely of the drug in unit time. It can be calculated by the ratio of the rate of elimination to the plasma concentration.

$$\text{Thus, CL} = \frac{\text{Rate of elimination}}{\text{Plasma concentration}}$$

Clearance is expressed as ml/litre/unit time.

Clearance is the most important factor determining drug concentration and should be considered when any drug is intended for long-term administration.

Drugs are metabolised/eliminated (elimination kinetics) from the body by:

1. First order kinetics: In first order kinetics (linear kinetics), a constant fraction of the drug is metabolised/eliminated per unit time. Most drugs follow first order kinetics and the rate of metabolism/excretion is dependent on their concentration in the body, i.e. it is exponential (Fig. 2.12). It also holds good for absorption of drugs.

2. Zero order kinetics (saturation kinetics or nonlinear kinetics): Here a constant amount of the drug present in the body is metabolised/eliminated per unit time. The amount remains same and does not increase with increase in dose.The metabolic enzymes get saturated and hence with increase in dose, the plasma drug level increases disproportionately resulting in toxicity. Such elimination is known as zero order kinetics.

Some drugs like phenytoin and warfarin are eliminated by both processes, i.e. by first order initially and by zero order at higher concentrations (**mixed order kinetics or Michaelis-Menten kinetics**). Hence, at higher doses, there is accumulation of the drug.

Examples of drugs that follow zero order kinetics:

- Alcohol
- Heparin
- Phenytoin
- Phenylbutazone.
- Aspirin

Plasma Half-life (t½)

Plasma half-life (t½) is the time taken for the plasma concentration of a drug to be reduced to half its value (Fig. 2.13). For example, if a particular dose of a drug is injected intravenously and its plasma concentration is found to be 100 µg/ml and the plasma concentration is estimated every hour and at the end of four hours it falls to 50 µg/ml, then the plasma half-life of the drug is four hours. Four to five half-lives are required for the complete elimination of a drug. Each drug has its own t½ and is an important pharmacokinetic parameter that guides the dosing

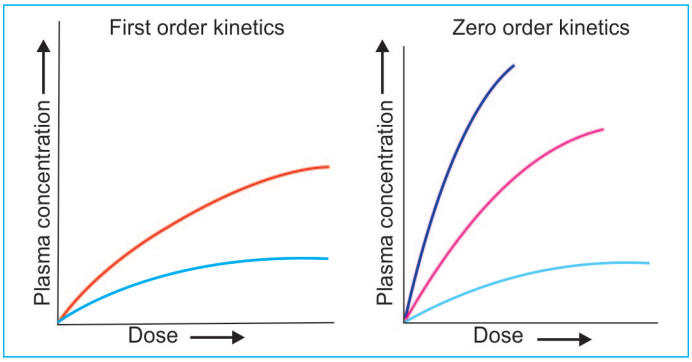


Fig. 2.12: First order kinetics: As the plasma concentration rises, metabolism and excretion proportionately increase. **Zero order kinetics:** In higher doses, the drug accumulates and the plasma concentration rises resulting in toxicity

Comparison between first order and zero order kinetics

Parameter	*First order*	*Zero order*
Definition	A constant fraction of drug is metabolized/eliminated per unit time	A constant amount of drug is metabolized per unit time
t½	Constant	Short at low and longer at high concentrations
Metabolism	Proportional to plasma concentration	Independent of plasma concentration
Higher doses	More drug gets metabolized → safer	Drug accumulates → toxicity
Drugs following	Most drugs	Few drugs, e.g. phenytoin, alcohol, aspirin

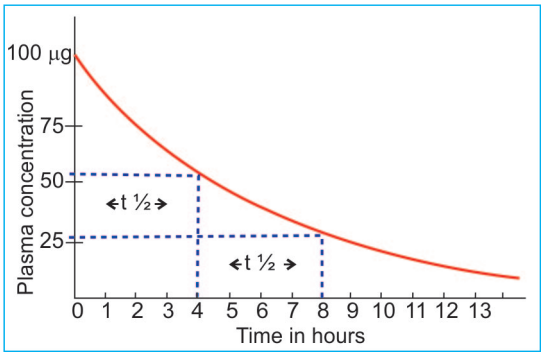


Fig. 2.13: Plasma concentration: Time curve following intravenous administration of a drug. Plasma t½ of the drug = 4 hours

regimen, e.g. esmolol has a t½ of 10 minutes, zolpidem 2 hours, aspirin 4 hours and chloroquine 10–24 days.

Significance of Plasma t½

Plasma t½ is necessary to know:

- The duration of action of the drug
- The frequency of administration
- The time needed for attainment of steady state concentration (SSC)—longer the t½, longer is the time needed to attain SSC.
- To calculate the loading and maintenance doses of the drug.

Factors Influencing Plasma t½

1. Plasma protein binding—drugs which are extensively bound to plasma proteins have a longer t½.
2. Enterohepatic circulation—increases the t½ of the drug.
3. Metabolism—faster the metabolism of a drug, shorter is its plasma t½.
4. Tissue storage—drugs which are sequestered in the tissues have a longer t½.
5. Clearance of the drug—drugs which are cleared faster have a shorter t½.

Biological half-life is the time required for total amount of drug in the body to be reduced to half.

Biological effect half-life is the time required for the biological effect of the drug to reduce to half. With some drugs, like propranolol, the pharmacological effect of the drug may last much longer, i.e. even after its plasma levels fall. In such drugs, biological effect half-life gives an idea of the duration of action of the drug.

Terminal half-life: On long-term use, certain drugs may remain in secondary compartments and they get gradually released into the circulation as the plasma concentration of drugs fall.

Steady-state concentration (SSC)

If a drug is administered repeatedly at short intervals before complete elimination, the drug accumulates in the body and reaches a 'state' at which the rate of elimination equals the rate of administration. This is known as the **'steady-state' or plateau level** (Fig. 2.14). After attaining this level, the plasma concentration fluctuates around an average steady level. It takes 4–5 half-lives for the plasma concentration to reach the plateau level. A drug with t½ >24 hr, if given daily, accumulates on prolonged use and could lead to toxicity. Hence for such drugs, once the SSC is attained, the dose given should be equal to the dose eliminated everyday. Steady-state plasma concentration (C_{pss}) can be obtained as follows:

$$C_{pss} = \frac{\text{Dose rate}}{\text{Clearance}}$$

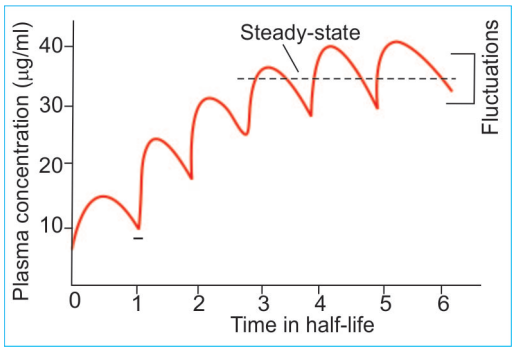


Fig. 2.14: Drug accumulation and attainment of steady-state concentration on oral administration

DRUG DOSAGE

Depending on the patient's requirements and the characteristics of the drug, drug dosage can be of the following kinds:

Fixed dose: In case of reasonably safe drugs, a fixed dose of the drug is suitable for most patients, e.g. analgesics like paracetamol—500 to 1000 mg 6 hourly is the usual adult dose.

Individualised dose: For some drugs especially the ones with low safety margin, the dose has to be 'tailored' to the needs of each patient, e.g. anticonvulsants, antiarrhythmic drugs.

Loading dose: In situations when target plasma concentrations have to be attained rapidly, a loading/bolus dose of the drug is given at the beginning of the treatment. A loading dose is a single large dose or a series of quickly repeated doses given to rapidly attain target concentration, e.g. heparin given as 5000 IU bolus dose. Once the target level is reached, a maintenance dose is sufficient to 'maintain the drug level' and to balance the elimination. Drugs with large V (e.g. chloroquine) and drugs with long t½ (e.g. digitoxin) need a long time to attain SSC and, therefore, need a loading dose. In emergencies, loading dose is often used to rapidly attain SSC for many drugs including the short t½ ones. Loading dose is calculated by:

$$\text{Loading dose} : \frac{\text{Target } C_p \times V}{F}$$

where, C_p is plasma concentration, *V* is volume of distribution and F is bioavailability.

The disadvantage with the loading dose is that the patient is rapidly exposed to high concentrations of the drug which may result in toxicity.

Maintenance dose is the dose given at constant intervals after the target C_{pss} is attained to maintain the steady state. The dose should be calculated to balance elimination, that is, the rate of administration should be equal to the rate at which it is eliminated.

Fixed Dose Combinations

When two or more drugs are combined to be given as a single preparation, it is called fixed dose combination (FDC). In these, both the drugs and the doses are fixed. There are hundreds of such FDCs available in the market. The rationale for giving any two drugs in a single formulation include:

1. Convenience of single pill and thereby better patient compliance, e.g. antitubercular drugs/antiretroviral drugs in a single tablet
2. Synergistic effect, e.g. cotrimoxazole, levodopa + carbidopa
3. To reduce adverse effects—thiazides with potassium sparing diuretics
4. Prevent development of resistance—antitubercular drugs.

Disadvantages

1. Reduced flexibility in dose adjustment
2. Difficulty to assess side effects
3. Increased risk of toxic effects—due to both drugs especially if there are overlapping side effects, e.g. hepatotoxicity due to INH, rifampicin and pyrazinamide.

Several rational and approved FDCs are available to improve patient compliance. They may be used in suitable patients, particularly when dose adjustments of individual drugs are not needed. However, hundreds of such FDCs are being marketed which are irrational, wasteful and often harmful. Use of such irrational FDCs should be avoided. For example:

- Amoxicillin + cloxacillin for staphylococcal infection
- Norfloxacin + metronidazole for diarrhoea
- Enalapril + losartan for hypertension.

Competency achievement: The student should be able to:

PH 1.2 Describe the basis of evidence-based medicine and **therapeutic drug monitoring**.[2]

THERAPEUTIC DRUG MONITORING

The response to a drug generally depends on the plasma concentration attained in the patient. This in turn depends on the bioavailability, volume of distribution and clearance. As these parameters vary among individuals, there is a wide variation in the plasma concentration attained from patient to patient. In some situations, it may be necessary to monitor treatment by measuring plasma drug concentrations. TDM may be done for such drugs in which plasma concentration correlates well with the effect. It should be done after steady state concentration is reached.

TDM is required for the following:

1. While using drugs with low safety margin to avoid therapeutic failure, e.g. digoxin, theophylline, lithium.
2. To reduce the risk of toxicity particularly when nephrotoxic drugs are used in renal failure, e.g. aminoglycosides.
3. When there are no reliable methods to assess benefit, e.g. antidepressants (TCAs).
4. To treat poisoning
5. When there is unexplainable therapeutic failure
6. To check patient compliance.

Therapeutic drug monitoring is **not required** for:

1. Drugs whose response can be easily measured chemically, e.g. blood pressure for antihypertensives.
2. 'Hit and run' drugs, whose effect persist for a long time even after the drug is eliminated, e.g. proton pump inhibitors like pantoprazole.
3. Drugs to which significant tolerance develops.
4. When estimation of plasma levels is too expensive, TDM should be restricted.

METHODS OF PROLONGING DRUG ACTION

In several situations, it may be desirable to use long-acting drugs, e.g. to avoid repeated

Table 2.5: Methods of prolonging duration of action of drugs

Processes	*Methods*	*Examples*
Pharmaceutical modification		
1. *Oral*	Sustained release preparations, controlled release preparation, coating with resins, etc.	Iron, deriphylline, diclofenac
2. *Parenteral*	1. Reducing solubility—oily suspension	Procaine + penicillin, benzathine penicillin
	2. Altering particle size	Depot progestins Insulin zinc suspension as large crystals that are slowly absorbed
	3. Pellet implantation—sialistic capsules	DOCA Testosterone
	4. Combining with protein	Protamine + zinc + insulin
	5. Chemical alteration—esterification	Estrogen, testosterone
3. *Topical*	Transdermal adhesive patches, ointments	Scopolamine, nitroglycerin
	Ocuserts (transmucosal)—used in eye	Pilocarpine
Pharmacokinetic intervention		
1. Absorption	Reducing vascularity of absorbing surface	Adrenaline + lignocaine (vasoconstrictor)
2. Distribution	Choosing more protein bound member of the group	Sulfonamides like sulfamethoxypyridazine
3. Metabolism	• Inhibiting the metabolising enzyme cholinesterase	Physostigmine—prolongs action of acetylcholine
	• By inhibiting the enzyme peptidase in renal tubular cells	Cilastatin—prolongs action of imipenem
4. Excretion	Competition for same transport system—for renal tubular secretion	Probenecid—prolongs the action of penicillin and ampicillin

doses and to avoid too much fluctuations in plasma concentration. When such drugs are not available, the duration of action of the available drugs may be prolonged (Table 2.5).

The duration of action of drugs can be prolonged by pharmaceutical intervention or by interfering with the pharmacokinetic processes, i.e. by:

1. Slowing absorption
2. Using a more plasma protein bound derivative
3. Inhibiting metabolism
4. Delaying excretion.

[1–2] From Medical Council of India, *Competency based Undergraduate Curriculum for the Indian Medical Graduate*, 2018;1:136–144.

CHAPTER 3

Pharmacodynamics

Competency achievement: The student should be able to:
PH 1.5 Describe general principles of mechanism of drug action.[1]

Pharmacodynamics is the study of actions of the drugs on the body and their mechanisms of action, i.e. to know what drugs do and how they do it.

Drugs produce their effects by interacting with the physiological systems of the organisms. By such interaction, drugs merely modify the rate of functions of the various systems. Drugs cannot bring about qualitative changes, i.e. they cannot change the basic functions of any physiological system. Thus drugs act by:

1. Stimulation
2. Depression
3. Irritation
4. Replacement
5. Anti-infective or cytotoxic action
6. Modification of immune status

Stimulation is the increase in activity of the specialised cells, e.g. adrenaline stimulates the heart.

Depression is the decrease in activity of the specialised cells, e.g. quinidine depresses the heart; barbiturates depress the central nervous system. Some drugs may stimulate one system and depress another, e.g. morphine depresses the CNS but stimulates the vagus.

Irritation can occur on all types of tissues in the body and may result in inflammation, corrosion and necrosis of cells.

Replacement: Drugs may be used for replacement when there is deficiency of natural substances like hormones, metabolites or nutrients, e.g. insulin in diabetes mellitus, iron in anaemia, vitamin C in scurvy.

Anti-infective and cytotoxic action: Drugs may act by specifically destroying infective organisms, e.g. penicillins, or by cytotoxic effect on cancer cells, e.g. anticancer drugs.

Modification of immune status: Vaccines and sera act by improving our immunity while immunosuppressants act by depressing immunity, e.g. glucocorticoids.

MECHANISMS OF DRUG ACTION

Most drugs produce their effects by binding to specific target proteins like receptors, enzymes and ion channels. Drugs may act on the cell membrane, inside or outside the cell to produce their effect. Drugs may act by one or more complex mechanisms of action. Some of them are yet to be understood. The fundamental mechanisms of drug actions may be:

1. Through receptors
2. Through enzymes and pumps
3. Through ion channels
4. Through transporters and symporters
5. By physical action
6. By chemical interaction
7. By altering metabolic processes.

1. *Through receptors:* A large number of drugs act by interacting with specific receptors in the body (*see* as follows).

2. *Through enzymes and pumps:* A large number of drugs act by inhibition of various enzymes, thus altering the enzyme-mediated reactions, e.g. allopurinol inhibits the enzyme xanthine oxidase;
   - Acetazolamide inhibits carbonic anhydrase;
   - Enalapril inhibits angiotensin-converting enzyme;
   - Aspirin inhibits cyclo-oxygenase, neostigmine inhibits acetylcholinesterase.

   Methotrexate binds DHFR with high affinity and inhibits it. Sildenafil inhibits phosphodiesterase-5 to cause vasodilatation. Several enzymes are influenced by drugs and this forms one of the common models of drug action.

   Membrane pumps, like H^+-K^+-ATPase may be inhibited by omeprazole and Na^+-K^+-ATPase by digoxin.
3. *Through ion channels:* Drugs may interfere with the movement of ions across specific channels either by opening or closing them. Such channels may be voltage-gated, ligand-gated or G-protein regulated channels, e.g.
   i. *Ca^{++} channels:*
      - Calcium channel blockers like verapamil block the voltage-sensitive L-type Ca^{++} channels in the myocardium.
      - Ethosuximide blocks T type Ca^{++} channels in thalamic neurons.

   ii. *K^+ channels:*
      - Nicorandil opens K^+ channels in the heart and vascular smooth muscles.
      - Sulfonylureas close the ATP sensitive K^+ channels in the pancreatic β cells to promote insulin release.

   iii. *Sodium channels:*
      - Lignocaine blocks the Na^+ channels to depress nerve conduction
      - Phenytoin blocks the Na^+ channels to stabilize neuronal membrane for antiepileptic activity.

   iv. *GABA-gated chloride channels:* Diazepam acts through $GABA_A$ receptor to increase the frequency of chloride channel opening in the neurons to cause CNS depression.
4. *Through transporters and symporters:* Many of the endogenous substances are transported across the biological membrane with the help of carriers. The action of several of the neurotransmitters is terminated by reuptake into the presynaptic nerve terminal. Drugs may act by blocking or inhibiting the movement of these transporters, symporters or antiporters. They are explained in detail in the respective chapters.

   Antidepressant imipramine acts by binding to transporters SERT and NET to inhibit the reuptake of serotonin and norepinephrine. Most diuretics act by influencing the movement of ions across the cells in the nephron by action on the symporters and transporters—thiazides inhibit Na^+-Cl^- symporter and furosemide inhibits Na^+-K^+-2Cl cotransporter.
5. *By physical action:* The action of a drug could result from its physical properties like:
   - Adsorption—A*ctivated charcoal in poisoning*
   - Mass of the drug—*bulk laxatives like psyllium, bran*
   - Osmotic property—*osmotic diuretics like* mannitol

     Osmotic purgatives like magnesium sulphate
   - Radioactivity—^{131}I
   - Radio-opacity:
     - *Barium sulphate*
     - *Contrast media.*
6. *By chemical interaction:* Drugs may act by chemical reaction.
   - Antacids—neutralise gastric acids
   - Oxidising agents—potassium permanganate and germicidal
   - Chelating agents—bind heavy metals making them nontoxic.
7. *By altering metabolic processes:* Drugs like antimicrobials alter the metabolic pathway in the micro-organisms resulting in destruction of the micro-organism, e.g. sulfonamides interfere with bacterial folic acid synthesis.

RECEPTOR

The works of **Langley** and **Ehrlich** put forth the concept of a 'receptor substance.' In the late 19th century, Langley noted that curare could oppose contraction of skeletal muscles caused by nicotine but did not block the contraction due to electrical stimulation. Paul **Ehrlich** observed that some organic chemicals had antiparasitic activity while others with slightly different structures did not have such activity. **Clark** put forward a theory to explain the drug action based on the drug-receptor occupation.

Last three decades have seen an explosion in our knowledge of the receptors. Various receptors have been identified, isolated and extensively studied.

Definition: A receptor is a macromolecular site on the cell with which an agonist binds to bring about a change.

Affinity: Affinity is the ability of a drug to bind to a receptor.

Intrinsic activity or efficacy: Intrinsic activity is the ability of a drug to elicit a response after binding to the receptor.

Agonist: An agonist is a substance that binds to the receptor and produces a response. It has both affinity and intrinsic activity, e.g. adrenaline is an agonist at α and β adrenergic receptors; morphine is an agonist at mu(μ) opioid receptors.

Antagonist: An antagonist is a substance that binds to the receptor and prevents the action of agonist on the receptor. It has affinity but no intrinsic activity. An antagonist has a structural similarity to the natural ligand for the receptor because of which the receptor identifies the antagonist as its ligand. Naloxone is an antagonist at μ opioid receptors. It binds to the receptor, has no effect by itself, but blocks the action of the opioid agonists like morphine. Tubocurarine is an antagonist at the nicotinic receptors. It blocks the receptors and prevents the action of acetylcholine on the receptors.

Partial agonist: A partial agonist binds to the receptor but has low intrinsic activity. Pentazocine is a partial agonist at μ opioid receptors, pindolol is a partial agonist at β-adrenergic receptors. A partial agonist occupies the receptor and brings about weak effects. It also blocks the action/binding of the full agonists. Thus a partial agonist is also called agonist–antagonist.

Inverse agonist: Some drugs, after binding to the receptors produce actions opposite to those produced by a pure agonist. They are known as inverse agonists, e.g. diazepam acting on benzodiazepine receptors produces sedation, anxiolysis, muscle relaxation and controls convulsions, while the inverse agonists β-carbolines bind to the same receptors to cause arousal, anxiety, increased muscle tone and convulsions.

Ligand: Ligand is a molecule which binds selectively to a specific receptor.

Spare receptors: In an experiment using adrenaline on rabbit aortic strips, Furchgott showed that the agonist occupied only a small percentage of receptors to produce maximum contraction. Some experiments showed that high concentration of an agonist can still produce maximal response in the presence of an irreversible antagonist and this was because of the presence of **'spare' or reserve receptors.** Thus it is possible to stimulate the myocardium even when 90% of the cardiac β-adrenergic receptors are blocked by an irreversible β-blocker.

Silent receptors: These are receptors to which an agonist binds but does not produce a response. Presence of such silent receptors may explain the phenomenon of tolerance. Plasma proteins that bind drugs are considered to act as silent receptors as they

just bind the drug and the drug is not available for action.

Site: The receptors may be present in the cell membrane, in the cytoplasm or on the nucleus.

Nature of receptors: Receptors are proteins.

Synthesis and lifespan: Receptor proteins are synthesized by the cells. They have a definite lifespan after which the receptors are degraded by the cell and new receptors are synthesized.

Functions of receptors: The two functions of receptors are:

1. Recognition and binding of the ligand.
2. Propagation of the message.

For the above functions, the receptor has two functional domains (areas):

1. A ligand-binding domain (LBD)—the site to bind the drug molecule or ligand.
2. An effector domain—which undergoes a change to propagate the message.

Several theories have been proposed to explain drug–receptor interaction. Drug–receptor interaction has been considered to be similar to **'lock and key'** relationship where the drug specifically fits into the particular receptor (lock) like a key. The **rate theory** proposes that the magnitude of response depends on the rate of agonist–receptor association and dissociation. The rate of receptor-binding is more initially but after it reaches the peak, there is a decrease.

The **occupation theory** suggests that the magnitude of drug response depends on the proportion of the receptors occupied by the drug. As per this theory, the response will progressively increase till a steady state is reached.

Receptor model: Currently, the drug–receptor interaction is explained by a 'two-state' model of the receptor. According to this, a receptor exists in two states, namely *resting or inactive (Ri)* and a*ctivated (Ra).* A drug with greater affinity for the activated state will function as a full agonist while that with moderate affinity for the activated state will be a partial agonist.

Interaction of the agonist with the receptor brings about changes in the receptor which in turn conveys the signal to the **effector system.** The final response is brought about by the effector system through **second messengers.** The agonist itself is the first messenger. The entire process involves a chain of events triggered by drug–receptor interaction. The transduction process which links the binding of the receptor and the actual response is called 'coupling'.

Receptor classification: International Union of Pharmacologists (IUPHAR) has setup expert working groups to classify receptors based on different criteria. For example, they have classified adrenergic and cholinergic receptors.

Receptor families: On stimulation of a receptor, the time required to elicit the response varies largely from a fraction of a second in some receptors to hours and days in others. This difference is because of the variation in mechanisms involved in linking the receptor and the effector systems (transduction mechanisms). Based on this, 5 types or super families of the cell surface receptors are identified. They are best understood with the help of Fig. 3.1.

The receptor types are:

1. G-protein-coupled receptors (metabotropic receptor)
2. Ion channel receptors (ionotropic receptor)
3. Transmembrane enzymatic receptors (kinase-linked receptor)
4. Transmembrane non-enzymes (cytokine and TLR).
5. Nuclear receptors (transcription factors or receptors that regulate gene transcription).

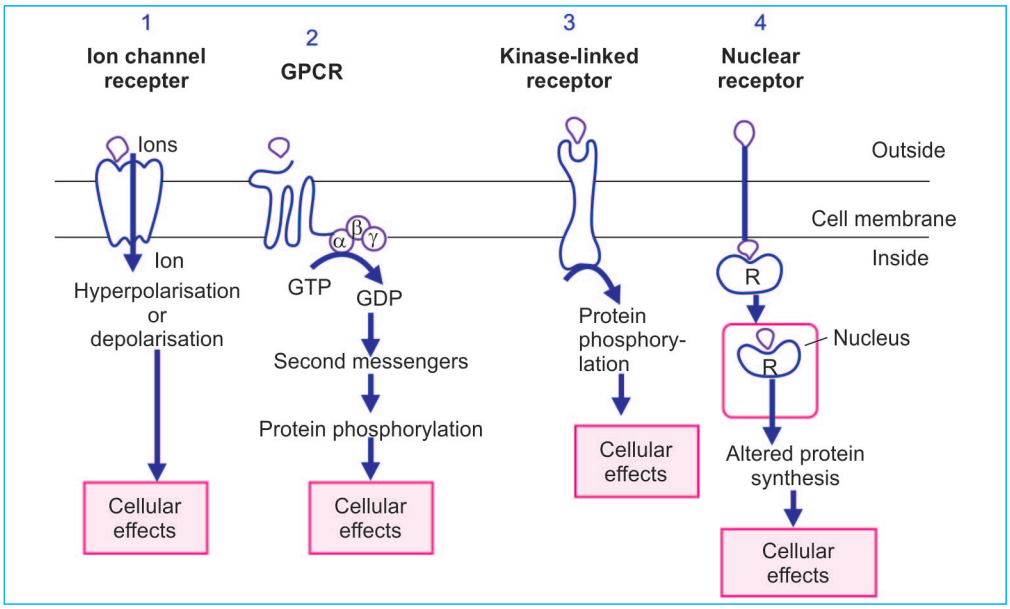


Fig. 3.1: Type 1: Binding of the agonist directly regulates the opening of the ion channel. Type 2: Agonist binding activates the receptor linked to an effector system by a G protein (G). Type 3: Agonist binding to extracellular domain activates enzymatic activity of its intracellular catalytic domain. Type 4: Agonist binds to the intracellular receptor, the complex moves to the nucleus and directs protein synthesis

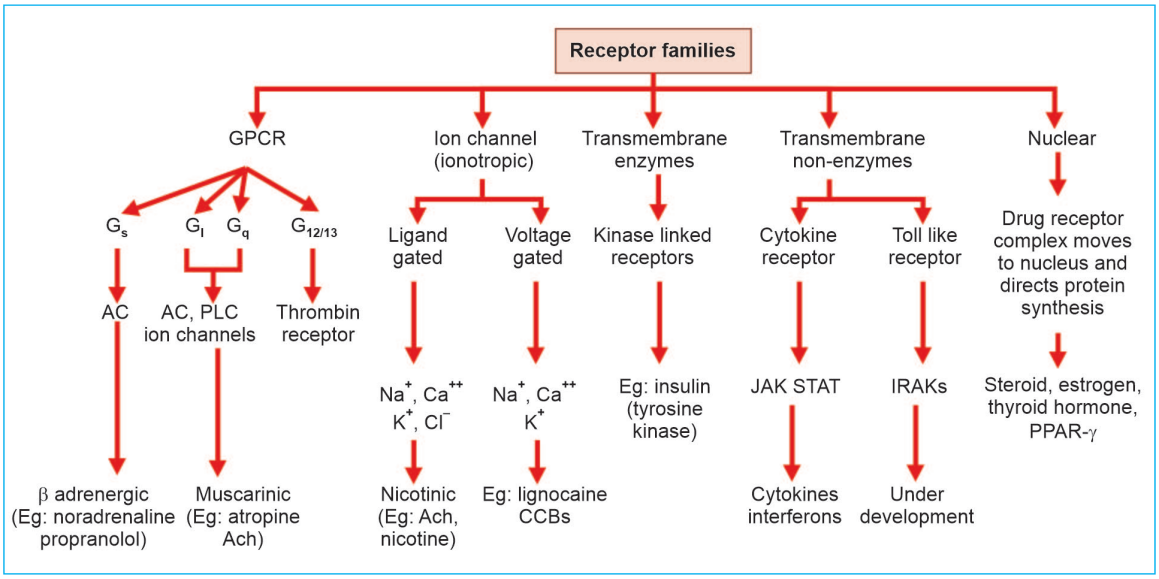
Receptor Families and their Signal Transduction Mechanisms (Flowchart 3.1)

1. **Ion channel receptors or receptor channels or ionotropic receptors** are proteins present on the cell surface or cell membrane. Binding of the agonist opens the channel allowing ions to cross the membrane. These are called **ligand-gated ion channels** and the ion channel acts as the target for the drug. Depending on the ion and the channel, depolarisation/hyperpolarisation occurs, e.g. nicotinic cholinergic receptor channel permits passage of Na^+ ions resulting in depolarisation while the benzodiazepines bind the GABA receptor-chloride channel complex and facilitate the opening of the channel. The chloride ions flow into the neurons and cause hyperpolarisation. Some examples are given in Table 3.1.
2. **G-protein-coupled receptors (GPCR)** are receptors that signal through G proteins and form a family of transmembrane proteins, present across the plasma membrane. The receptor consists of 7α helices (Fig. 3.1). The G proteins are bound to the inner face of the plasma membrane and form a complex with (coupled to) the receptor. They are called G proteins because of their interaction with guanine nucleotides GTP and GDP. G proteins act as signal transducers, that is, they convey the information to the effector system when

Table 3.1: Drugs acting through ion channel receptors

Ion channels	*Drug*	*Action*
Na^+ channel	Lignocaine	Blockade
	Quinidine	Blockade
	Acetylcholine	Opening
Ca^{++} channel	Nifedipine	Blockade
	Verapamil	
K^+ channel	Sulfonylureas	Blockade
	Nicorandil	Opening
Cl^- channel	Diazepam	Opening
	Barbiturates	Opening (GPCR)

Flowchart 3.1: Receptor families and their transduction mechanisms



an agonist binds to the GPCR. The G-proteins consist of three subunits, viz. α, β and γ (called heterotrimer meaning 3 different subunits) with GDP bound to a subunit (Fig. 3.2a). The G proteins act as signal transducers, i.e. they convey the information to the effector system. When a ligand binds to the G-protein-coupled receptor, the associated G-protein gets activated. This in turn activates adenylyl cyclase or phospholipase C to generate the respective second messengers. These second messenger systems are called effector pathways. The second messengers include cAMP, IP_3, DAG, Ca^{++} and cGMP. G-proteins acting through second messengers, bring about a chain of intracellular changes. Thus G-proteins act as links or mediators between the receptor and the effector systems. The α subunit possesses GTPase activity. G-proteins are of different classes like G_s, G_i, G_q, G_o and $G1_{12/13}$. G_s is stimulatory and G_i is inhibitory. For example, G_s activation opens Ca^{++} channels in myocardium and skeletal muscles while Gi opens K^+ channels in the heart and smooth muscles. Adrenergic

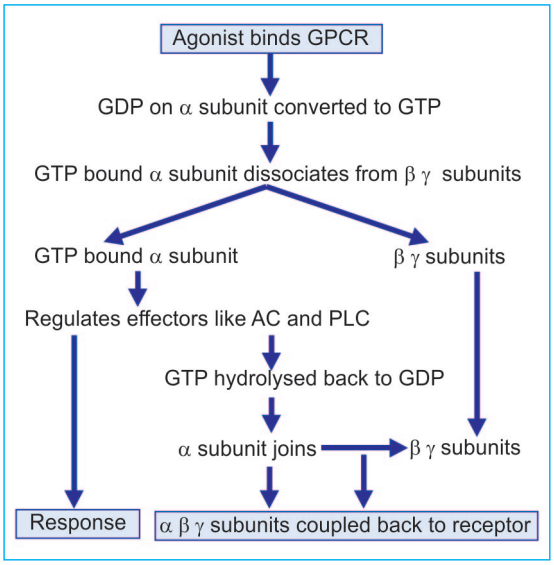


Fig. 3.2a: Functioning of GPCRs

receptors and muscarinic cholinergic receptors are examples of G-protein-coupled receptors.

Effector pathways through which the G-protein-coupled receptors work are:

- Adenylyl cyclase/cAMP pathway
- Phospholipase C/IP_3-DAG pathway
- Ion channel regulation.

Second messenger pathways for some GPCRs

Pathway	*Second messenger*	*Receptors*
Adenylyl cyclase	↑cAMP	β, D1, H2, V2
	↓cAMP	α_2, D2, M2, μ, 5HT1
PLC	IP3-DAG	α_1, M1, M2, 5HT2
Ion channels	↑Ca^{++}	β_1
	↓Ca^{++}	D2, κ opioid
	↑K^+	α_2, D2, $GABA_B$, δ opioid

- *Adenylyl cyclase pathway* (Fig. 3.2b): Stimulation of adenylyl cyclase results in the formation and accumulation of cAMP within the cell. This cAMP acts through protein kinases which phosphorylate various proteins to regulate the cell function. The response may be contraction, relaxation, lipolysis or hormone synthesis.
- *Phospholipase C/IP_3-DAG pathway* (Fig. 3.3): Activation of phospholipase C (PLC) results in the formation of second messengers IP_3 and DAG from the membrane phospholipids phosphoinositol pyrophosphate (PIP_2). IP_3 mobilises Ca^{++} from intracellular depots and this Ca^{++} mediates responses like secretion, contraction, metabolism and hyperpolarization. DAG activates protein kinase C (PKC) which regulates cell function.

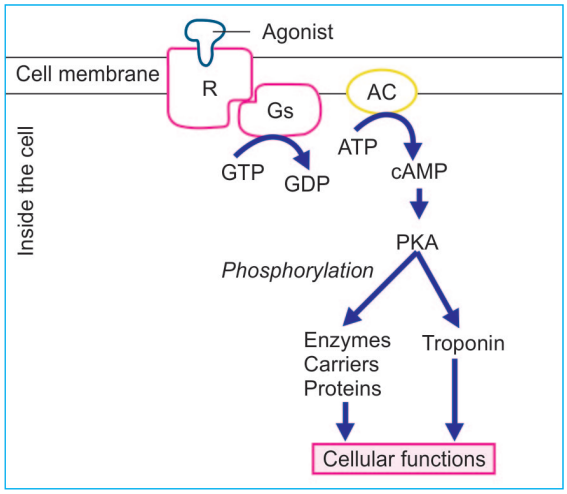


Fig. 3.2b: G-protein-coupled receptor—transduction through adenylyl cyclase pathway with cAMP as second messenger. R = Receptor, G_s = G-protein (stimulatory)

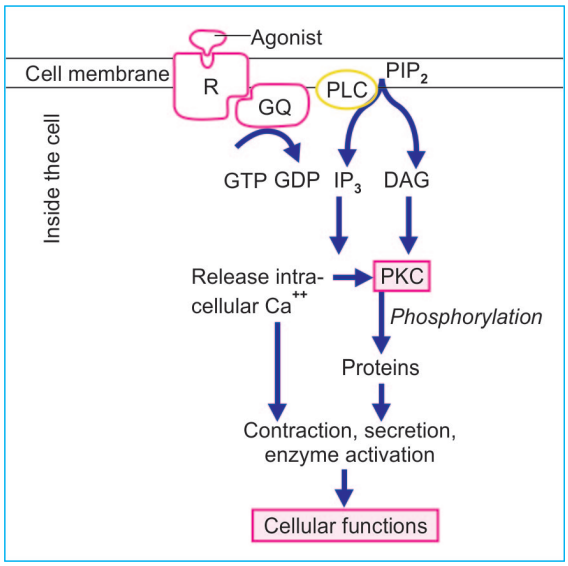
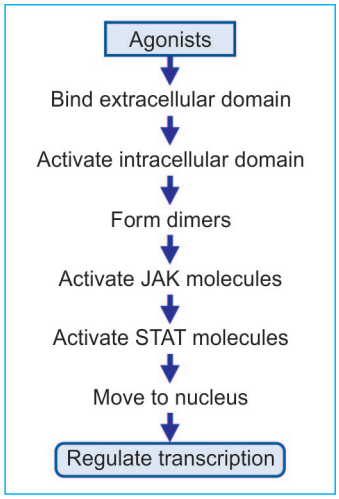


Fig. 3.3: G-protein-coupled receptor acting through the second messengers IP_3 and DAG. CaM-calmodulin

- *Ion channel regulation:* The activated G-proteins can also directly (without the help of second messengers) convey the signal to some ion channels of calcium and potassium causing opening or closing of the channels. The resulting responses include depolarisation/hyperpolarisation.

3. **Enzymatic receptors** are transmembrane proteins with an extracellular domain (site) for ligand binding and intracellular domain to carry out the catalytic activity and the two domains are linked by a single peptide chain. They are protein kinases and hence are also known as **kinase-linked receptors**. Binding of the agonist to the ligand binding domain results in autophosphorylation of the intracellular domain. This in turn triggers phosphorylation of various intracellular proteins resulting in the characteristic response, e.g. receptors of insulin, leptin and growth factors including epidermal growth factors and platelet-derived growth factors.
4. A type of non-enzymatic receptor is the **JAK-STAT binding receptor**. When an agonist binds to the extracellular domain, it activates the intracellular domain (which



forms dimers, i.e. groups of two) and mobile JAK (Janus kinase) molecules are activated. These molecules in turn activate signal transducers and activation of transcription-molecules (STAT-molecules). STAT-molecules move to the nucleus and regulate transcription, e.g. growth hormones, cytokines, interferons.

5. **Receptors that regulate gene transcription** are also called transcription factors or nuclear receptors. They are intracellular proteins which are in an inactive state. Binding of the agonist activates the receptor. The agonist-receptor complex moves to the nucleus where it interacts with DNA, regulates gene transcription and thereby directs the synthesis of specific proteins to regulate the activity of target cells. Examples are receptors for steroidal hormones, thyroid hormones, vitamin D and retinoids.

Receptor Regulation

The number of receptors (density) and their sensitivity can be altered in many situations. Denervation or prolonged deprivation of the agonist or constant action of the antagonist, all result in an increase in the number and sensitivity of the receptors. This phenomenon is called **upregulation.** Prolonged use of a β adrenergic antagonist, like propranolol, results in upregulation of β adrenergic receptors.

On the other hand, continued stimulation of the receptors causes desensitisation and a decrease in the number of receptors—known as **downregulation** of the receptors.

Clinical Consequences and Implications of Receptor Regulation

Upregulation: After prolonged administration, a receptor antagonist should always be tapered. For example, if propranolol, a β adrenoceptor blocker is suddenly withdrawn after long-term use, it precipitates angina. This

COMPARE AND CONTRAST
Receptor regulation

Upregulation	Downregulation
Prolonged deprivation of agonists or Constant use of antagonists or Denervation ↓ ↑ number of receptors, ↑ sensitivity ↓ ↑↑ response	Prolonged use of agonists or Continued stimulation of receptors ↓ ↓ number of receptors, ↓ sensitivity ↓ ↓↓ response
Eg: Angina following sudden withdrawal of β blockers after prolonged use	Eg: Reduced response to β_2 agonists after prolonged use in bronchial asthma

is because of upregulation of β receptors. Normal amounts of noradrenaline released during any stress can stimulate the heart and cause angina. This is because of upregulation of beta receptors. Normal amounts of noradrenaline released during any stress can stimulate the heart and cause angina.

Downregulation: Constant use of β adrenergic agonists in bronchial asthma results in reduced therapeutic response due to down-regulation of β_2 receptors develop tolerance.

DOSE RESPONSE RELATIONSHIP

The clinical response to the increasing dose of the drug is defined by the shape of the dose response curve (DRC). Initially, the extent of response increases with increase in dose till the maximum response is reached.

There are 2 types of dose response relationships, viz. **graded dose response relationship** and **quantal dose response relationship**. The graded dose response curve has the shape of a rectangular **hyperbola** (Fig. 3.4). After the maximum effect has been obtained, further increase in doses does not increase the response. If the dose is plotted on a logarithmic scale, the curve becomes **sigmoid** (Fig. 3.5).

Advantages of plotting log DRC are:

1. Wide range of doses can be displayed on the graph.
2. Easy to compare agonists and study antagonists.

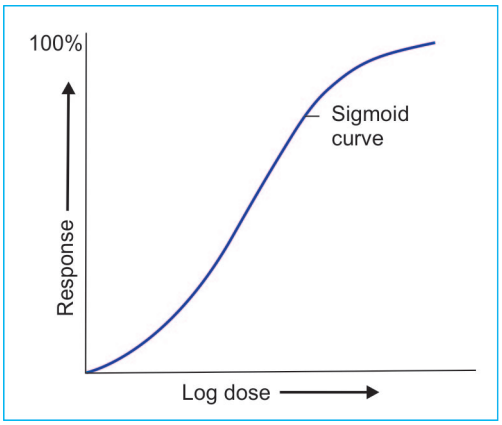


Fig. 3.5: Log dose response curve

The slope of DRC (Fig. 3.6) has clinical significance. A steep slope indicates that a small increase in dose produces a large increase in response, e.g. loop diuretics. Such drugs are more likely to cause toxicity and, therefore, individualisation of dose is required. A relatively flat DRC indicates that with an increase in dose, there is little increase in the response, e.g. thiazide diuretics. For such drugs, standard doses can be given to most patients.

Quantal DRC: Certain responses can only be all-or-none (e.g. vomiting) and when represented on the dose response curve, the curve appears bell-shaped (*see* Fig. 2.5, page 24) and it indicates the percentage of responders.

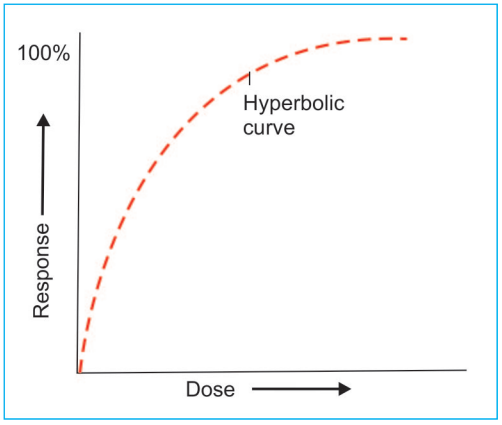


Fig. 3.4: Dose response curve

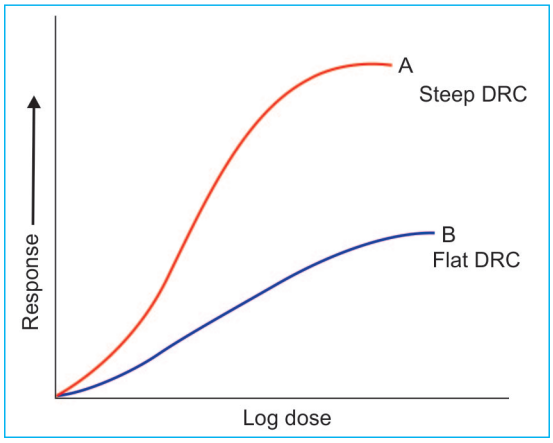


Fig. 3.6: Steep and flat dose response curves

Drug Potency

The amount of drug required to produce a response indicates the potency. For example, 1 mg of bumetanide produces the same diuresis as 50 mg of frusemide. Thus bumetanide is more potent than frusemide. In Fig. 3.7, drugs A and B are more potent than drugs C and D, drug A being the most potent and drug D the least potent. Hence higher doses of drugs C and D are to be administered as compared to drugs A and B. Generally, potency is of little clinical significance unless very large doses of the drug needs to be given due to low potency.

Maximal Efficacy

Efficacy indicates the maximum response that can be produced by a drug, e.g. frusemide produces powerful diuresis, not produced by any dose of amiloride. In Fig. 3.7, drugs B and C are more efficacious than drugs A and D. Drug A is more potent but less efficacious than drugs B and C. Such differences in efficacy are of great clinical importance.

Therapeutic Index

The dose response curves for different actions of a drug could be different. Thus salbutamol may have one DRC for bronchodilation and another for tachycardia. The distance between beneficial effect DRC and unwanted effect DRC indicates the safety margin of the drug (Fig. 3.8).

Median lethal dose (LD_{50}): Dose which is lethal to 50% of the population.

Median effective dose (ED_{50}): Dose that produces a desired effect in 50% of the test population.

Therapeutic index (TI) in experimental animals is obtained by the ratio of the median lethal dose to the median effective dose.

$$\text{Therapeutic index} = \frac{LD_{50}}{ED_{50}}$$

- TI gives an idea about the safety of the drug.
- The higher the therapeutic index, the safer is the drug.
- TI varies from species to species.
- For a drug to be considered reasonably safe, its TI must be >1.
- Penicillin, amoxicillin, diazepam, and atenolol have a high TI and their dose response curve is relatively flat.
- Llithium, digoxin, theophylline, barbiturates and carbamazepine have low TI and their DRC is steep.

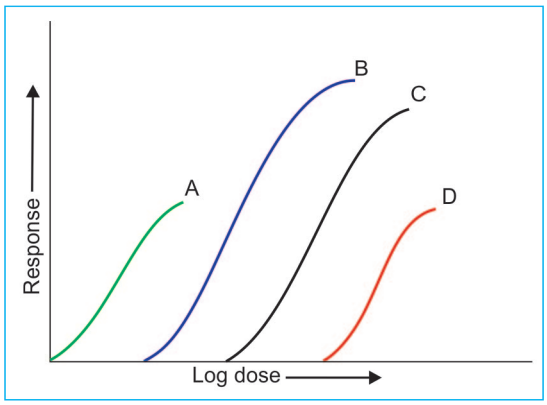


Fig. 3.7: Dose response curves of four drugs showing different potencies and maximal efficacies. Drug A is more potent but less efficacious than B and C. Drug D is less potent and less efficacious than drugs B and C

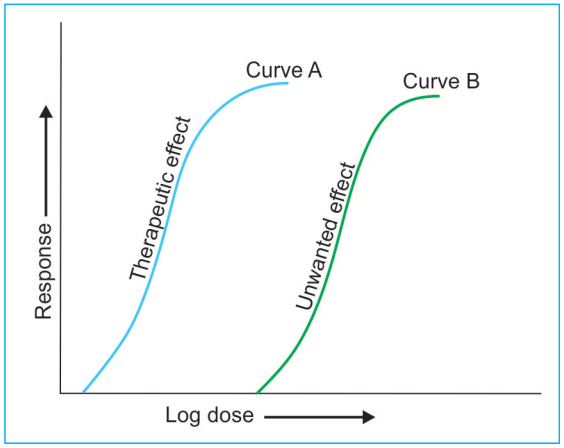


Fig. 3.8: The distance between the curves A and B indicates safety margin or therapeutic index (TI) of the drug. The greater the distance, more selective is the drug

- TI may be different for each action of a drug. For example, TI of aspirin used for headache is different from its TI for inflammation.

Limitations of Therapeutic Index

Therapeutic index does not consider idiosyncratic responses that result in toxicity. Moreover, the data is based on animal studies which may be difficult to apply on human beings and considers only 50% of a given set of animals. To get a more certain idea about safety, the drug should be effective in 99% and lethal to 1% of the test population. Such an index is called **certain safety factor.**

Thus, certain safety factor = $\frac{LD_1}{ED_{99}}$.

In human population, LD_{50} cannot be obtained and, therefore, ED_{50} is considered.

Therapeutic Window

Therapeutic window is the range of plasma concentrations below which the drug is ineffective and above which toxicity appears (therapeutic range). Hence, it is desirable to have the plasma concentration of drugs within this optimal therapeutic range in order to derive therapeutic effect without significant toxic effects. Therapeutic index quantifies the therapeutic window, i.e. if therapeutic window is small, TI is also small. Drugs with low therapeutic index have a narrow therapeutic window, e.g. the plasma drug levels of digoxin is 0.8–1.2 ng/ml, lithium 0.5–1.3 mEq/l, carbamazepine 3–10 µg/ml and clonidine 0.2–2 ng/ml. Imipramine produces optimum therapeutic effect only when its plasma levels are maintained between 50 and 200 ng/ml. Doses of such drugs must be titrated carefully.

DRUG SYNERGISM AND ANTAGONISM

When two or more drugs are given concurrently, the effect may be additive, synergistic or antagonistic.

Additive Effect

The effect of two or more drugs get added up and the total effect is equal to the sum of their individual actions.

Examples

Ephedrine + theophylline in bronchial asthma; nitrous oxide + ether as general anaesthetics.

Synergism

When the action of one drug is enhanced or facilitated by another drug, the combination is synergistic. In Greek, *ergon* = work; *syn* = with. Here, the total effect of the combination is greater than the sum of their independent effects. It is often called 'potentiation' or 'supra-additive' effect.

Examples

- Acetylcholine + physostigmine
- Levodopa + carbidopa.

Thus additive effect can be understood as 2 + 2 = 4 while synergistic effect is 2 + 2 = 5!

Antagonism

One drug opposing or inhibiting the action of another is antagonism. Based on the mechanisms, antagonism can be (Fig. 3.9):

1. *Chemical Antagonism*

Two substances interact chemically to result in inactivation of the effect, e.g. chelating agents inactivate heavy metals like lead and mercury to form inactive complexes; antacids like aluminium hydroxide neutralize gastric acid.

2. *Physiological Antagonism*

Two drugs act at different sites to produce opposing effects. For example, histamine acts on H_1 receptors to produce bronchospasm and hypotension while adrenaline reverses these effects by acting on adrenergic receptors.

Insulin and glucagon have opposite effects on the blood sugar level.

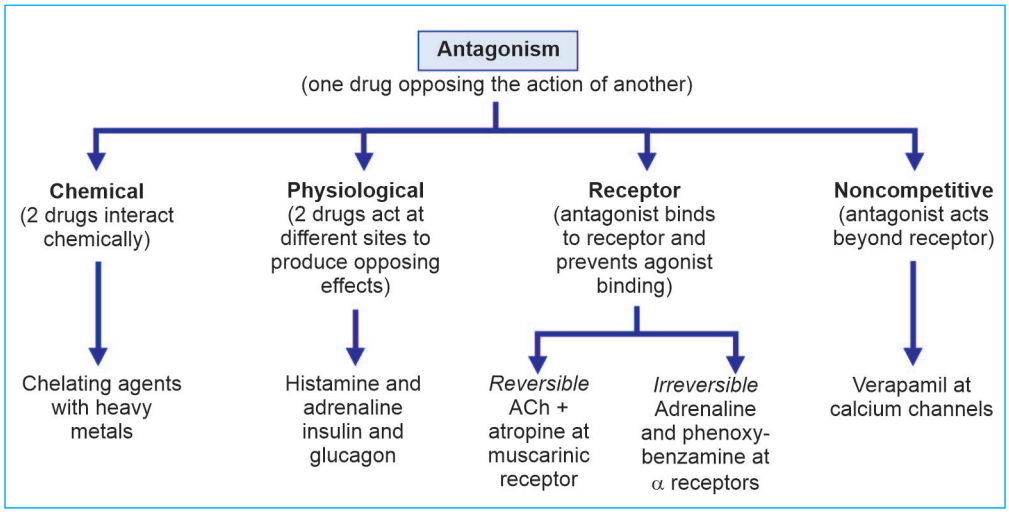


Fig. 3.9: Types of antagonism with examples

3. Antagonism at the Receptor Level

The antagonist binds to the receptor and inhibits the binding of the agonist to the receptor. Such antagonism may be reversible or irreversible.

Reversible or competitive antagonism: The agonist and antagonist compete for the same receptor. When a fixed concentration of an agonist is employed and the dose of the antagonist is progressively increased, the response to the agonist is progressively diminished. However, by increasing the concentration of the agonist, the antagonism can be overcome. It is thus reversible antagonism. The same maximal response can still be obtained by increasing the dose of the agonist. It is also called **surmountable** or **equilibrium type** of antagonism. This is the most common type of antagonism. Acetylcholine and atropine compete at muscarinic receptors. The antagonism can be overcome by increasing the concentration of acetylcholine at the receptor. Tubocurarine and acetylcholine compete for the nicotinic receptors at the neuromuscular junction. The dose response curve of the agonist shifts to the right (Fig. 3.10) in the presence of competitive antagonists.

Clinical significance: When an antagonist is used therapeutically, it should be borne in mind that the extent of inhibition brought about by a reversible antagonist depends on the concentration of the agonist. Therefore, the dose of the antagonist should be adjusted to get the optimum response, e.g. propranolol is used to block β adrenergic receptors. An increased amount of the endogenous agonists noradrenaline and adrenaline are released in stress and the dose of the antagonist (propranolol) needed would also be more in such situations.

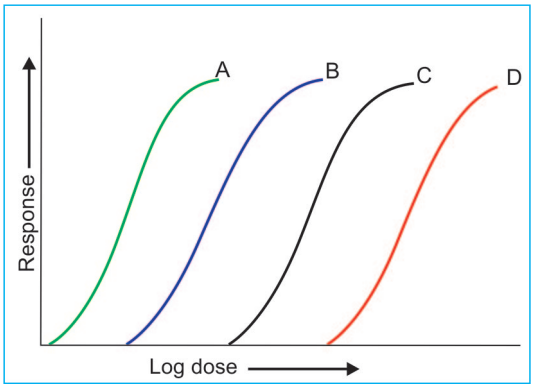


Fig. 3.10: Dose response curves of an agonist: A in the absence of competitive antagonist; B, C and D in the presence of increasing doses of a reversible competitive antagonist

Irreversible antagonism: The antagonist binds by covalent bonds to the receptor and it binds so firmly that it dissociates very slowly or not at all. Thus it blocks the action of the agonist and the blockade cannot be overcome by increasing the dose of the agonist and hence it is irreversible antagonism. In this type of antagonism, the duration of action is usually long since the effect remains till the new receptors are synthesized, e.g. adrenaline and phenoxybenzamine at alpha adrenergic receptors. This antagonism is also called **non-equilibrium** type of antagonism.

There is progressive flattening of the dose response curve (Fig. 3.11).

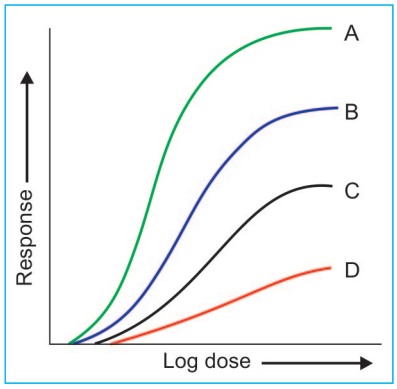


Fig. 3.11: Dose response curves of an agonist A, in the absence of antagonist, B, C, and D in the presence of increasing doses of an irreversible antagonist

4. Noncompetitive Antagonism

The antagonist blocks at the level of the receptor–effector linkage, i.e. at a different site beyond the receptor and not on the receptor. There is flattening as well as some rightward shift of the dose response curve (Fig. 3.12). For example, verapamil blocks the cardiac calcium channels and inhibits the entry of Ca^{++} during depolarisation. It thereby antagonises the effect of cardiac stimulants like isoprenaline and adrenaline. Since non-competitive antagonism is often confused with irreversible antagonism, they are compared in the table (below).

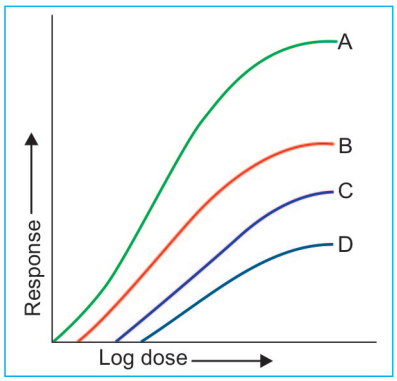


Fig. 3.12: Non-competitive antagonism—there is flattening as well as some rightward shift of DRC

FACTORS THAT MODIFY THE EFFECTS OF DRUGS

The same dose of a drug can produce different degrees of response in different patients and even in the same patient under different situations. Various factors modify the response to a drug. They are:

1. Body weight: The recommended dose is calculated for medium built persons. For the obese and underweight persons, the dose has to be calculated individually. Though body surface area is a better parameter for more accurate calculation of the dose, it is inconvenient and hence not generally used.

COMPARE AND CONTRAST

Parameter	*Irreversible antagonism*	*Non-competitive antagonism*
Receptor binding	Yes	Not involved
Mode of action	Binding irreversible or very long lasting	Binding at a different site than receptor
Example	Phenoxybenzamine at α receptors	Verapamil at Ca^{++} channels
DRC	Progressive flattening	Flattening and rightward shift

Formula:

$$\text{Dose} = \frac{\text{Body weight (kg)} \times \text{average adult dose}}{70}$$

2. Age: The pharmacokinetics of many drugs change with age resulting in altered response in extremes of age.

Newborn and infants: In the newborn, the liver and kidneys are not fully mature to handle the drugs, e.g. chloramphenicol can produce grey baby syndrome. The blood–brain barrier is not well-formed and drugs can easily reach the brain. The gastric acidity is low, intestinal motility is slow, skin is delicate and is permeable to drugs applied topically. Hence calculation of the appropriate dose, depending on the body weight is important to avoid toxicity. Also pharmacodynamic differences could exist, e.g. barbiturates which produce sedation in adults may produce excitation in children.

Formula for calculation of dose for children.

1. *Young's formula*

$$\text{Child's dose} = \frac{\text{Age (years)}}{\text{Age} + 12} \times \text{Adult dose}$$

2. Dilling's formula

$$\text{Child's dose} = \frac{\text{Age}}{20} \times \text{Adult dose}$$

In the elderly, the capacity of the liver and kidney to handle the drug is reduced and they are more susceptible to adverse effects. Hence, lower doses are recommended, e.g. elderly are at a higher risk of ototoxicity and nephrotoxicity by streptomycin.

3. Sex: There are no gross gender differences in response to drug. However, the hormonal effects and smaller body size may influence the drug response in women. Special care is necessary while prescribing for pregnant and lactating women and during menstruation. For example, purgatives cause pelvic congestion and if they are administered during menstruation, they may increase the menstrual blood loss.

Adult male rats metabolize drugs at a much faster rate than their female counterparts.

4. Species and race: Response to drugs may vary with species and race. For example, rabbits are resistant to atropine. Such variation makes it difficult to extrapolate the results of animal experiments. Variation in response to drugs is also noted among different races. Blacks need higher doses of atropine to produce mydriasis. The antipsychotic clozapine may cause a higher incidence of agranulocytosis in people of Finland. Hence most countries now approve a drug to be used in their country only after it has undergone trials on its own population.

5. Diet and environment: Food interferes with the absorption of many drugs and such drug–food interactions should be borne in mind. For example, tetracyclines form complexes with calcium present in the food and are poorly absorbed.

Polycyclic hydrocarbons present in the cigarette smoke may induce microsomal enzymes resulting in enhanced metabolism of some drugs. Examples of drug–food interactions:

Absorption increased by food—spironolactone, chloroquine, riboflavin, lithium, albendazole.

Absorption reduced by food—ampicillin, rifampicin, tetracycline, INH.

6. Route and time of administration: Occasionally route of administration may modify the pharmacodynamic response, e.g. magnesium sulphate given orally is a purgative. But given IV it causes CNS depression and has anticonvulsant effects for which it is used in eclampsia of pregnancy. Applied topically (poultice), it reduces local oedema. Hypertonic magnesium sulphate retention enema reduces intracranial tension.

N-acetylcysteine is another similar example. When given orally and IV it acts as an antidote in paracetamol overdosage—acetylcysteine replenishes glutathione stores

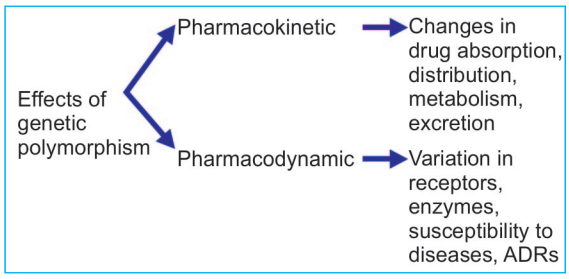
in the liver. If inhaled as a solution, it acts as a mucolytic while if irrigated into the urinary bladder, it counters cystitis caused by cyclophosphamide.

Time of administration: There are several diurnal variations in the body and the time of drug administration is important to obtain the benefit of such variations. For example, secretion of glucocorticoids is highest in the morning. Hence, if exogenous glucocorticoids are also administered in the morning, the HPA axis suppression is much less. The study of such correlation of drug effects to the circadian rhythm has emerged as chronopharmacology (*see* page 73).

7. Genetic factors: Variations in an individual's response to drugs could be genetically mediated. **Pharmacogenetics** is the study of genetically mediated variations in drug responses. Variation in nucleotide sequences could result in differences in response to drugs.

Competency achievement: The student should be able to:
PH 1.60 Describe and discuss pharmacogenomics and pharmacoeconomics.[2]

Pharmacogenomics and pharmacogenetics are often used to mean the same (as synonyms) but difference is pharmacogenetics deals with monogenetic variants while pharmacogenomics involves the entire spectrum of genes that could modify drug response.



Genetic **polymorphisms/variations** could result in changes in pharmacokinetics or pharmacodynamics.

i. ***Pharmacokinetic variations:*** Production of drug metabolizing enzymes is genetically controlled and variations are common.

Examples

a. *Oxidation of drugs* genetic polymorphism in cytochrome P450 enzymes result in variation in the rate of metabolism (oxidation, hydroxylation) of drugs metabolised by these enzymes, e.g. SSRIs, phenytoin, warfarin.

b. *Acetylation of drugs:* The rate of drug acetylation differs among individuals who may be fast or slow acetylators, e.g. INH, sulfonamides, hydralazine, procainamide and dapsone are metabolized by acetylation. Slow acetylators treated with hydralazine are more likely to develop lupus erythematosus.

c. *Atypical pseudocholinesterase:* Succinylcholine is metabolised by the enzyme pseu-docholinesterase. Some people inherit an atypical pseudocholinesterase which cannot quickly metabolise succinylcholine. When succinylcholine is given to such people, they develop a prolonged apnoea due to persistant action of succinylcholine.

ii. *Pharmacodynamic variations:* Variations in receptor, enzymes, susceptibility to ADRs and diseases:

a. *G6PD deficiency:* Deficiency of G6PD in RBCs leads to NADPH deficiency resulting in accumulation of glutathion. Exposure of such RBCs to drugs like primaquine, sulphones, and quinolones leads to hemolysis.

b. *Malignant hyperthermia:* Halothane and succinylcholine can trigger malignant hyperthermia in some genetically predisposed individuals (*see* pages 131, 190).

c. *Hepatic porphyrias:* Some people lack an enzyme required for haeme synthesis, and this results in accumulation of porphyrin-containing haeme precursors. Some drugs,

like barbiturates, griseofulvin and carbamazepine, induce the enzyme required for porphyrin synthesis resulting in accumulation of porphyrins. In both the above cases, neurological, gastrointestinal and behavioural abnormalities can occur due to excess porphyrins.

8. Dose: It is fascinating that the response to a drug may be modified by the dose administered. Generally as the dose is increased, the magnitude of the response also increases proportionately till the 'maximum' is reached. Further increases in doses may with some drugs produce effects opposite to their lower-dose effect, e.g.

i. In myasthenia gravis, neostigmine enhances muscle power in therapeutic doses, but in high doses it causes muscle paralysis.
ii. Physiological doses of vitamin D promotes calcification while hypervitaminosis D leads to decalcification.

Pharmacoeconomics *see* page 73.

9. Diseases: Presence of certain diseases can influence drug responses, e.g.

- *Gastrointestinal diseases:* Drugs are poorly absorbed in malabsorption syndrome.
- *Liver diseases:* Rate of drug metabolism including first pass metabolism is reduced due to dysfunction of hepatocytes. Also protein binding is reduced due to low serum albumin, because albumin is synthesized in the liver and blood levels of the free form of the drug increases in liver failure.
- *Cardiac diseases:* In CCF, there is oedema of the gut mucosa and decreased perfusion of liver and kidneys. These may result in cumulation and toxicity of drugs like propranolol and lignocaine.
- *Renal dysfunction:* Drugs mainly excreted through the kidneys are likely to accumulate and cause toxicity, e.g. streptomycin, amphotericin B. Doses of such drugs need to be reduced. Several drugs are totally eliminated unchanged only by the kidneys and such drugs can cause more toxicity. Also, the diseased kidneys are more susceptible to the toxic effects of nephrotoxic drugs like gold, penicillamine and aminoglycosides.
- *Endocrine diseases:* Hypothyroid patients are more sensitive to the effects of certain drugs like CNS depressants. Patients with benign prostatic hypertrophy are more susceptible to urinary retention with anticholinergics and tricyclic antidepressants.

10. Repeated dosing: Repeated dosing can result in:

a. Cumulation
b. Tolerance
c. Tachyphylaxis
d. Resistance

a. *Cumulation:* Drugs like digoxin which are slowly eliminated may cumulate resulting in toxicity.

b. *Tolerance:* It is the requirement of higher doses of a drug to produce a given response. Tolerance may be natural or acquired.

- *Natural tolerance:* The species/race shows less sensitivity to the drug, e.g. rabbits show tolerance to atropine; black race are tolerant to mydriatics.
- *Acquired tolerance* develops on repeated administration of a drug. The patient who was initially responsive becomes tolerant, e.g. tolerance develops to barbiturates, opioids, nitrites.

Tolerance may develop to some actions of the drug and not to others, e.g. morphine—tolerance develops to analgesic and euphoric effects of morphine but not to its constipating and miotic effects. Barbiturates—tolerance develops to sedative but not antiepileptic effects of barbiturates.

Table 3.2: Compilation of some useful examples

Drugs that are almost completely absorbed on oral ingestion (~100% bioavailability)
- Diazepam
- Chlordiazepoxide
- Lithium
- Salicylic acid
- Digitoxin
- Minocycline
- Valproic acid
- Indomethacin
- Phenobarbitone
- Linezolid

Drugs that undergo extensive first pass metabolism
- Propranolol
- Lignocaine
- Verapamil
- Pentazocine
- Nitroglycerin
- Testosterone
- Hydrocortisone
- Metoprolol
- Chlorpromazine
- Morphine
- Pethidine
- Insulin
- Isoprenaline
- Levodopa

Drugs that are highly bound to plasma proteins
- Warfarin
- Diazepam
- Phenylbutazone
- Indomethacin
- Clofibrate
- Phenytoin
- Sulfonamides
- Salicylates
- Tolbutamide
- Frusemide

Absorption increased by fatty food
- Halofantrine
- Albendazole
- Atovaquone
- Griseofulvin
- Efavirenz
- Posaconazole

Apparent volume of distribution (V_d)

Low V_d drugs	*High V_d drugs*
• Heparin	• Pethidine
• Warfarin	• Digoxin
• Aminoglycosides	• Chloroquine
• Aspirin	• Nortriptyline
• Furosemide	• Fluoxetine
• Ampicillin	• Haloperidol
• Amoxicillin	• Amiodarone

Some microsomal enzyme inducers
- Phenobarbitone
- Rifampicin
- Tolbutamide
- Phenylbutazone
- DDT
- Carbamazepine
- Phenytoin
- Griseofulvin
- Metronidazole
- Cigarette smoke
- Alcohol

Some microsomal enzyme inhibitors
- Cimetidine
- Erythromycin
- Omeprazole
- Grape fruit juice
- Allopurinol
- Fluoxetine
- Quinidine
- Ketoconazole
- Chloramphenicol

Some folate antagonists
- Sulfonamides
- Trimethoprim
- Methotrexate
- Pemetrexed
- Pyrimethamine
- Proguanil
- Dapsone

Prodrugs
- Levodopa → Dopamine
- Prednisone → Prednisolone
- Enalapril → Enalaprilat
- Bacampicillin → Ampicillin
- Cortisone → Hydrocortisone
- Azathioprine → Mercaptopurine
- Cyclophosphamide → Aldophosphamide
- Zidovudine → Zidovudine triphosphate

Hit and run drugs
- Reserpine
- Omeprazole

Drugs metabolised by zero-order kinetics
- Alcohol
- Salicylates
- Phenylbutazone
- Phenytoin
- Heparin

Drugs that undergo enterohepatic recycling
- Tetracyclines
- Doxorubicin
- Mefloquine
- Indomethacin
- Estradiol
- Amphetamine
- Metronidazole
- Morphine
- Phenytoin

Drugs available as transdermal patches
- Nitroglycerin
- Fentanyl
- Testosterone
- Hyoscine
- Estrogen

Drugs to which tolerance develops easily
- Nitrates
- Barbiturates
- Hydralazine
- Opioids

Agents which exhibit tachyphylaxis
- Ephedrine
- 5-HT
- Amphetamine
- Tyramine

Drugs which need tapering (after long-term use)
- β-blockers
- Antiepileptics
- Sedatives
- Antipsychotics
- Glucocorticoids
- Clonidine
- Antidepressants

Contd...

Table 3.2: Compilation of some useful examples (*contd...*)

Drugs with very short t½ (2–10 min)

- Dobutamine
- Dopamine
- Esmolol
- Adenosine
- Sodium nitroprusside
- Alteplase
- 5-Fluorouracil

Drugs with long t½

Drug	*t½ in days*
Chloroquine	10–24
Etanercept	3–4
Phenylbutazone	3–4
Mefloquine	16–24
Gold salts	7
Suramin	90

Some haemodialysable drugs

- Isoniazid
- Barbiturates
- Methaqualone
- Phenytoin
- Theophylline
- Ethyl and methyl alcohol
- Amphetamines
- Lithium
- Salicylates

Histamine liberators

- Morphine
- Pentamidine
- Hydralazine
- Tubocurarine
- Vancomycin
- Amphetamine

Drugs that colour urine

Orange red

- Rifampicin
- Phenazopyridine
- Daunorubicin
- Vitamin B complex (yellow)
- Nitazoxanide (green)

Nitric oxide donors

- Sodium nitroprusside
- Nitrates
- Nitrites

Drugs with low therapeutic index

- Digoxin
- Theophylline
- Lithium
- Quinidine

Drugs which need plasma concentration monitoring

- Lithium
- Digoxin
- Aminoglycosides
- Carbamazepine
- Theophylline

Some teratogenic drugs

- Thalidomide
- Sodium valproate
- Carbamazepine
- Lithium
- Androgens
- Progestins
- Anticancer drugs
- Tetracyclines
- Phenytoin
- Phenobarbitone
- Glucocorticoids
- Oestrogens
- Antithyroid drugs

Drugs to be used with caution in renal failure

- Aminoglycosides
- Cyclosporine
- Foscarnet
- Ifosfamide
- ACE inhibitors
- Anticancer drugs like cisplatin, methotrexate
- Amphotericin
- Acyclovir
- Pentamidine
- NSAIDs
- Sulphonamides
- Penicillamine

Drugs that can produce gingival hyperplasia

- Phenytoin
- Calcium channel blockers
- Cyclosporin

Drugs that can induce haemolysis in G6PD deficient patients

- Sulfonamides
- Nitrofurans
- Vitamin K analogs
- Some vegetables
- Primaquine
- NSAIDs
- Dapsone

Drugs excreted in saliva

- Clarithromycin
- Phenytoin
- Metoclopramide
- Metronidazole
- Disulfiram

Mechanisms: The mechanisms of development of tolerance could be of two types:

Tolerance
- Pharmacokinetic mechanisms
- Pharmacodynamic causes

Pharmacokinetic: Changes in absorption, distribution, metabolism and excretion of drugs may result in reduced concentration of the drug at the site of action and is also known as **dispositional tolerance**, e.g. barbiturates induce microsomal enzymes and enhance their own metabolism.

Pharmacodynamic: Changes in the target tissue, may make it less responsive to the drug. It is also called **functional tolerance**. It could be due to downregulation of receptors as in

opioids or due to compensatory mechanisms of the body, e.g. blunting of response to some antihypertensives due to salt and water retention.

Cross tolerance is the development of tolerance to pharmacologically related drugs, i.e. to drugs belonging to a particular group. Thus chronic alcoholics also show tolerance to barbiturates and general anaesthetics.

c. *Tachyphylaxis:* It is the rapid development of tolerance. When some drugs are administered repeatedly at short intervals, tolerance develops rapidly and is known as tachyphylaxis or acute tolerance, e.g. ephedrine, amphetamine, tyramine and 5-hydroxytryptamine. This is thought to be due to depletion of noradrenaline stores as the above drugs act by displacing noradrenaline from the sympathetic nerve endings. Other mechanisms involved may be slow dissociation of the drug from the receptor thereby blocking the receptor. Thus ephedrine given repeatedly in bronchial asthma may not give the desired response.

d. ***Resistance:*** Repeated administration of an antibiotic can result in reduced or no response to it and this could lead to life-threatening infections (*see* page 533).

11. Psychological factor: The doctor–patient relationship influences the response to a drug often to a large extent by acting on the patient's psychology. The patient's confidence in the doctor may itself be sufficient to relieve a suffering, particularly the psychosomatic disorders. This can be substantiated by the fact that a large number of patients respond to placebo. **Placebo** is the inert dosage form with no specific biological activity but only resembles the actual preparation in appearance (dummy medication).

Placebo = 'I shall be pleasing' (in Latin).

Placebo medicines are used in:

i. Clinical trials as a control to compare and assess whether the new compound is significantly better than the placebo.

ii. To benefit or please a patient psychologically when he does not actually require an active drug as in mild psychosomatic disorders and in chronic incurable diseases.

In fact all forms of treatment including physiotherapy and surgery have some placebo effect. The effect of placebo is influenced by the **personality** of the treating doctor, personality of the **patient** and the **formulation** of placebo used. Placebo can release endorphins in the brain to provide analgesia. The ability of the doctor to instill confidence in the patient itself carries enough weightage and the skill should be developed right from the student days as part of medical education. Some people are more likely to respond to placebo and are called **placebo reactors**. The formulation given as placebo should appear 'impressive'. **Injections** seem to have more pronounced 'placebo effect' than oral preparations. Substances used as placebo include **lactose**, **some vitamins**, **minerals** and **distilled water injections**. Placebo can **release endorphins** in the brain produce analgesia. However, the effect of placebo may not be consistant or could be temporary.

Nocebo: When an established drug fails to produce its known therapeutic effect, it is often referred to as 'nocebo' effect which means it is opposite to that of 'placebo'. It could be because the patient lacks faith in the drug or doctor.

Psychological factor thus plays an important role in therapeutics.

12. Presence of other drugs: The concurrent use of two or more drugs can influence the response of each other (*see* Drug Interactions, page 66).

Patient Compliance

For the success of any treatment, good patient compliance is essential.

Patient compliance is considered 'good' when the patient strictly follows the treatment related instructions given by the

doctor. It may vary from partial compliance to total noncompliance. Compliance is an important factor which influences treatment.

Various factors which determine the patient compliance are:

1. Inadequate education—unable to understand the instructions, particularly complex regimen
2. Adverse effects—particularly disturbing ADRs
3. Polypharmacy (multiple drugs)—some drugs may be missed.
4. Lack of confidence in doctors
5. Financial—may be unable to afford
6. Disease—psychiatric illness or false belief

Directly observed treatment short course (DOTS) is a strategy to ensure good compliance to antitubercular drugs where a health worker supervises the tablet being swallowed.

[1–2] From Medical Council of India, *Competency based Undergraduate Curriculum for the Indian Medical Graduate*, 2018;136–144.

CHAPTER 4

Adverse Drug Reactions, Pharmacovigilance and Drug Interactions

Competency achievement: The student should be able to:

PH 1.6 Describe principles of pharmacovigilance and ADR reporting systems.[1]

PH 1.7 Define, identify and describe the management of adverse drug reactions (ADR).[2]

ADVERSE DRUG REACTIONS

All drugs can produce unwanted effects. WHO has defined an adverse drug reaction as "any response to a drug that is noxious and unintended and that occurs at doses used in man for prophylaxis, diagnosis or therapy." All drugs can cause adverse effects. Some patients are more likely to exhibit adverse effects to drugs.

Adverse drug reactions are classified (Fig. 4.1) as follows:

Type A (or augmented) reactions are related to the known pharmacological effects of the drug and are **predictable**, dose-related and quantitative adverse effects. For example, hypotension following alpha-blockers, insulin-induced hypoglycaemia, bleeding following anticoagulants. Most ADRs are of this category and are mostly reversible by dose reduction or stopping the drug. Type A

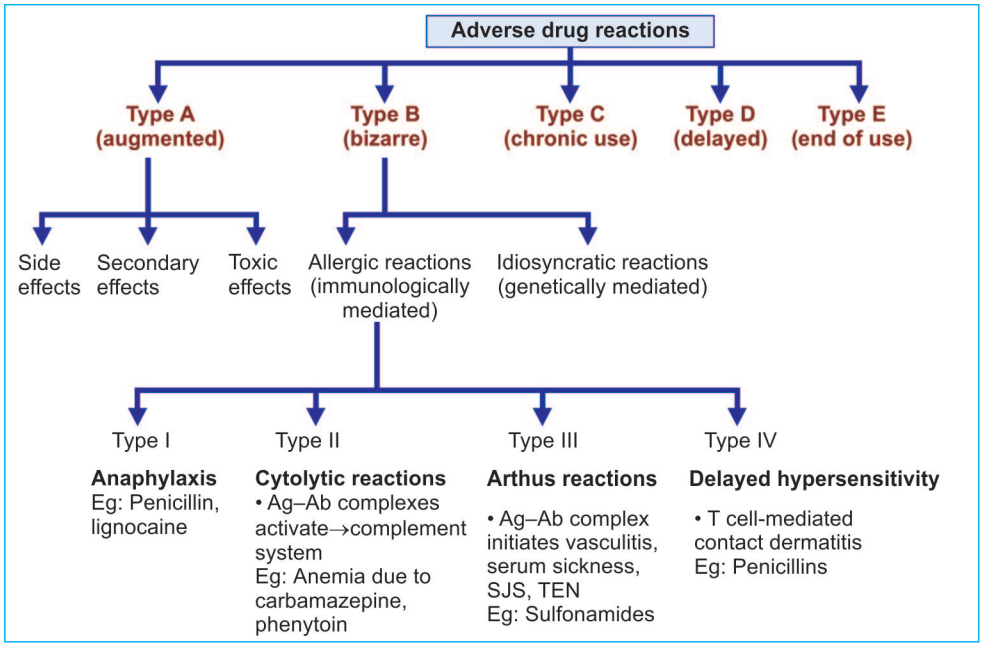


Fig. 4.1: Classification of ADRs

reactions include side effects, secondary effects and toxic effects.

a. *Side effects:* Side effects are unwanted effects of a drug that are an extension of the pharmacological effects and are seen with the therapeutic dose of the drug. They are predictable, common and can occur in all people, e.g. hypoglycaemia due to insulin; hypokalaemia following frusemide.

b. *Secondary effects:* Secondary effects are the indirect consequences of a primary drug action. Examples include superinfection on treatment of a primary infection by broad-spectrum antibiotics.

c. *Toxic effects:* Toxic effects are seen with higher doses of the drug and can be serious, e.g. morphine causes respiratory depression in overdosage which can be fatal (*see* Toxicology, Chapter 60).

Type B (bizarre) reactions are unrelated to the primary pharmacological effects of the drug and are, therefore, not predictable. They are less common, not tolerated and are an abnormal reaction to the drug. They could be idiosyncratic (genetically mediated) reactions or allergic reactions (immunologically mediated).

- **Idiosyncrasy** is a genetically determined abnormal reaction to a drug, e.g. primaquine and sulfonamides induce haemolysis in patients with G6PD deficiency; some patients show excitement with barbiturates. In addition, some responses like chloramphenicol-induced agranulocytosis, where no definite genetic background is known, are also included under idiosyncrasy. In some cases, the person may be highly sensitive even to low doses of a drug (e.g. a single dose of quinine can produce cinchonism in some) or highly insensitive even to high doses of the drug.
- **Allergic reactions** to drugs (*see* below) are immunologically-mediated reactions which are not related to the therapeutic effects of the drug. The drug or its metabolite acts as an antigen to induce antibody formation. Subsequent exposure to the drug may result in allergic reactions. The manifestations of allergy are seen mainly on the target organs, viz. skin, respiratory tract, gastrointestinal tract, blood and blood vessels.

Type C (continuous or chronic use) reactions occur on prolonged use of drugs and both dose and duration of drug use influence these ADRs. For example, chloroquine retinopathy, Cushing's syndrome, analgesic nephropathy.

Type D (delayed effects)—occur long after stopping treatment, sometimes after years. For example, leukaemia following treatment of Hodgkin's lymphoma; teratogenic effects.

Type E (end of use): These effects are due to sudden discontinuation of a drug after prolonged use. For example, acute adrenal insufficiency after sudden cessation of glucocorticoids, angina after sudden withdrawal of atenolol. Withdrawal syndrome to opioids and other drugs of abuse also are categorized as type E ADRs.

Pharmacovigilance

See page 65.

DRUG ALLERGY

Drugs can induce allergic reactions which could range from mild itching to anaphylaxis. They can induce both types of allergic reactions, viz. humoural and cell-mediated immunities. Mechanisms involved in Types I, II and III reactions are humoural immunity while Type IV reactions are due to cell-mediated immunity.

Types of Allergic Reactions and their Mechanisms

Type I (anaphylactic) reactions: The drug induces the synthesis of IgE antibodies which are fixed to the mast cells. On subsequent exposure, the antigen–antibody complexes cause degranulation of mast cells releasing

the mediators of inflammation like histamine, leukotrienes, prostaglandins and platelet-activating factor. These are responsible for the characteristic signs and symptoms of anaphylaxis like bronchospasm, laryngeal oedema and hypotension which could be fatal. Allergy develops within minutes and is called immediate hypersensitivity reaction, e.g. penicillins. Skin tests may predict this type of reactions. Penicillins, cephalosporins, lignocaine, procaine, iron dextran and streptomycin are some drugs known to cause anaphylaxis.

Type II (cytolytic) reactions: The drug binds to a protein and together they act as antigens and induce the formation of antibodies. The antigen–antibody complexes activate the complement system resulting in cytolysis causing thrombocytopenia, agranulocytosis and aplastic anemia. Examples are carbamazepine, phenytoin, sulfonamides and phenylbutazone. Mismatched blood transfusion reactions are also cytolytic reactions.

Type III (Arthus) reactions: The antigen binds to circulating antibodies and the complexes are deposited on the vessel wall where it initiates the inflammatory response resulting in vasculitis. Rashes, fever, arthralgia, lymphadenopathy, serum sickness and Stevens-Johnson syndrome are some of the manifestations of arthus type reaction. **Serum sickness** is characterized by fever, arthritis, nephritis, oedema and skin rashes. Penicillins, sulfonamides, phenytoin, streptomycin and heparin can cause serum sickness. **Stevens-Johnson syndrome** (SJS) is characterized by severe bullous erythema multiforme particularly in the mucous membranes with fever and malaise. **Toxic epidermal necrolysis** (TEN) is the most serious form of drug allergy with mucocutaneous reactions that can be fatal. Aminopenicillins, sulfonamides, sulfones, phenytoin, barbiturates, carbamazepine, phenylbutazone and quinolones are the drugs associated with SJS and TEN. Both SJS and TEN involve mucocutaneous manifestations but the extent of involvement is greater in TEN.

Type IV (delayed hypersensitivity) reactions: This type of reactions is mediated by T lymphocytes and macrophages. The antigen reacts with receptors on T lymphocytes which produce lymphokines leading to a local allergic reaction, e.g. contact dermatitis in nurses and doctors handling penicillins and local anaesthetics.

Prevention of allergic reactions: In order to prevent allergic reactions, it is important to take history of drug allergy. If such a history is present, the drug as well as its chemically related drugs should be avoided. For drugs which are known to cause allergy like penicillins and cephalosporins, sensitivity skin test should be done before administering the full therapeutic dose.

Drugs Likely to Cause Allergy

Penicillins	Sulphonamides (and other sulpha drugs)
Cephalosporins	Salicylates
Radio contrast media (with iodine)	Quinolones
Antisera	Local anesthetics

Desensitization: Hyposensitization or desensitization is required for some drugs like penicillin G when there are not many alternatives available. To start with, very small doses of the drug is given repeatedly at short intervals to desensitize and the dose is then gradually increased as the patient gets desensitized.

Other forms of adverse drug reactions:

1. *Drug intolerance:* Drug intolerance is the inability of a person to tolerate a drug even in therapeutic doses and is unpredictable. It could be quantitative or qualitative. Quantitative intolerance is when patients show exaggerated response to even small doses of the drug, e.g. vestibular dysfunction after a single dose of streptomycin may be seen in some patients. Intolerance could

also be qualitative, e.g. idiosyncrasy and allergic reactions.

2. *Iatrogenic diseases (physician-induced):* These are drug-induced diseases. Even after the drug is withdrawn, its toxic effects can persist, e.g. isoniazid-induced hepatitis; chloroquine-induced retinopathy. Drugs that can induce parkinsonism are chlorpromazine, haloperidol and other phenothiazines, metoclopramide and reserpine.
3. *Photosensitivity:* Drugs could sensitize the skin to sunlight and the UV rays of the sun.
4. *Drug dependence:* Drugs that influence the behaviour and mood are often misused to obtain pleasurable effects. Repeated use of such drugs results in dependence. Several words, like drug abuse, addiction and dependence, are used confusingly. Drug dependence is a state of compulsive use of drugs in spite of the knowledge of the risks associated with their use. It is also referred to as drug addiction. Dependence could be 'psychologic' or 'physical' dependence. Psychologic dependence is compulsive drug-seeking behaviour to obtain its pleasurable effects, e.g. cigarette smoking. Physical dependence is said to be present when withdrawal of the drug produces adverse symptoms. The body undergoes physiological changes to adapt itself to the continued presence of the drug in the body. Stopping the drug results in 'withdrawal syndrome.' The symptoms of withdrawal syndrome are disturbing and the person then craves for the drug, e.g. alcohol, opioids and barbiturates (*see* page 277).

   Mild degree of physical dependence is seen in people who drink too much of coffee.
5. *Teratogenicity:* Teratogenicity is the ability of a drug to cause foetal abnormalities when administered to a pregnant woman. *Teratos* in Greek means monster. The sedative thalidomide taken during early pregnancy for relief from morning sickness resulted in thousands of babies being born with phocomelia (seal limbs). This thalidomide disaster (1958–61) opened the eyes of drug licensing authorities and various nations made it mandatory to conduct strict teratogenicity tests before a new drug is approved for use.

   Depending on the stage of pregnancy during which the teratogen is administered, it can produce various abnormalities.

   - Conception to 16 days—usually resistant to teratogenic effects. If affected, abortion occurs.
   - Period of organogenesis (17 to 55 days of gestation): Most vulnerable period; major physical abnormalities occur.
   - Foetal period (56 days onwards)—period of growth and development—hence developmental and functional abnormalities result.

   Therefore, in general, drugs should be avoided during pregnancy specially in the first trimester. The type of malformation also depends on the drug, e.g. thalidomide causes phocomelia; tetracyclines cause deformed teeth; sodium valproate causes spina bifida. Drugs are categorised based on their teratogenic potential as given in Table 4.1.
6. *Carcinogenicity and mutagenicity:* Some drugs can cause cancers and genetic abnormalities. For example, anticancer drugs can themselves be carcinogenic; other examples are radioactive isotopes and some hormones.
7. *Organ toxicities:* Drugs can also cause toxicity to various **organ systems** (Table 4.2).

Hepatotoxicity: Liver is the major organ of drug metabolism and most drugs are metabolized by it. Drug-induced hepatotoxicity is a serious problem accounting for nearly 10% of all cases of hepatitis. It is also a common cause of acute hepatic failure. Hepatotoxicity can complicate treatment because it can result in reduced metabolism of drugs, which in turn increases their plasma levels, further worsening toxicity.

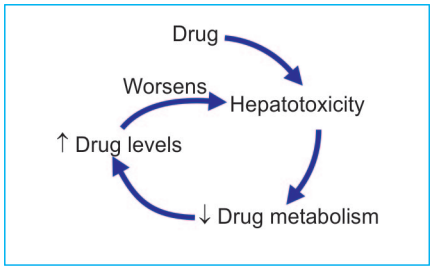
Drug-induced hepatotoxicity could be:

1. *Dose dependent:* Hepatocellular, e.g. a metabolite of paracetamol generates free

Table 4.1: Teratogenicity risk categories (general interpretation in brackets for simplification)

Category	*Features*
A	Studies in women have failed to demonstrate risk to the fetus, e.g. chloroquine (safe)
B	Risk not confirmed in humans (animal studies do not show teratogenic potential), e.g. paracetamol, amoxicillin (mostly safe)
C	Teratogenic in animal studies but inadequate human data. Drug used only if benefits outweigh risk to fetus, e.g. glucocorticoids (likely to be safe)
D	Evidence of risk in humans but benefit in mother may need the drug as in life-threatening disease, e.g. phenytoin (likely to be teratogenic)
X	Evidence of risk; drug contraindicated in pregnancy, e.g. thalidomide, isotretinoin (teratogenic)

radicals which in small amounts will be detoxified by glutathione conjugation. In larger doses glutathione stores get depleted and toxic metabolites get accumulated loading to liver cell injury. Toxic doses of paracetamol cause fatal fulminant hepatic failure.



2. *Non-dose-dependent hepatocellular damage:* Drugs like halothane, isoniazid, NSAIDs, ethambutol, antiepileptics like valproic acid and phenytoin and many other drugs are known to cause liver toxicity which is not dose related and could be an idiosyncratic reaction.
3. *Fatty liver:* Chronic alcoholism and drugs like glucocorticoids, methotrexate, indomethacin, bleomycin and tamoxifen can cause fatty liver. Triglycerides get accumulated in the liver which may lead to inflammation called steatohepatitis.
4. *Chronic active hepatitis:* Drugs like isoniazid, paracetamol, nitrofurantoin, halothane and hydralazine can cause prolonged hepatitis with altered liver enzymes. This could be due to autoantibodies against the antigens specific to the liver in genetically

Table 4.2: Examples of drugs affecting various organ systems

Organ system affected	*Examples*
1. Hepatotoxicity	Isoniazid, pyrazinamide, paracetamol, chlorpromazine, 6-mercaptopurine, halothane, ethanol, phenylbutazone
2. Nephrotoxicity	Analgesics, aminoglycosides, cyclosporine, cisplatin, cephalexin, penicillamine, gold salts
3. Ototoxicity	Aminoglycosides, frusemide
4. Ocular toxicity	Chloroquine, ethambutol
5. Gastrointestinal system	Opioids, broad-spectrum antibiotics
6. Cardiovascular system	Digoxin, doxorubicin
7. Respiratory system	Aspirin, bleomycin, busulfan, amiodarone, methotrexate
8. Musculoskeletal system	Corticosteroids, heparin
9. Behavioural toxicity	Corticosteroids, reserpine
10. Neurological system	INH, haloperidol, ethambutol, quinine, doxorubicin vincristine
11. Dermatological toxicity	Doxycycline, sulfonamides, gold, d-penicillamine
12. Electrolyte disturbances	Diuretics, mineralocorticoids
13. Hematological toxicity	Chloramphenicol, sulfonamides
14. Endocrine disorders	Methyldopa, oral contraceptives
15. Sexual dysfunction	Prazosin, reserpine, anticholinergics, barbiturates, methyldopa, tricyclic antidepressants

predisposed individuals. If not treated on time, it may progress to cirrhosis.

5. *Cholestasis:* Obstruction to the secretion of bile from the liver may result in jaundice. It may be seen following use of estrogen, anabolic steroids, glibenclamide and rifampicin. Long-term cholestasis may lead to cholestatic hepatitis with hepatocellular damage. *Examples:* Erythromycin, carbamazepine, some NSAIDs and sulphonamides.

Signs and Symptoms

Raised liver enzymes, jaundice, hepatomegaly and vomiting

Examples of drugs	*Hepatotoxic effect*
Paracetamol	Hepatic necrosis
Erythromycin, rifampicin	Cholestatic jaundice
Pyrazinamide, isoniazid, halothane	Hepatitis
Alcohol	Cirrhosis

Factors Contributing to Hepatotoxicity

1. Age—more common in infants and elderly patients.
2. Gender—women are more at risk of hepatotoxicity due to drugs like methyldopa, erythromycin (in pregnancy).
3. Genetics and race—variations in the drug metabolizing enzymes may be responsible for some races being at risk of drug-induced hepatotoxicity. For example, people could be fast acetylators (INH t½ 1 hr) or slow acetylators (INH t½ 3–5 hours) of INH, based on their genetic inheritance. Slow acetylators respond better to INH but hepatotoxicity is more likely in them.
4. Dose and duration of use—higher the dose and longer the use, risk of hepatotoxicity is higher.
5. Pre-existing liver disease—patients who are suffering from liver diseases are more likely to be affected by hepatotoxic drugs.

Precautions

- Drugs which are known to cause hepatotoxicity should be used carefully.
- Lowest effective dose should be used.
- Combination of 2 or more hepatotoxic drugs should be avoided.
- Liver function tests should be done at regular intervals to monitor the status.

TREATMENT OF DRUG OVERDOSAGE

See Chapter 60.

PHARMACOVIGILANCE

Competency achievement: The student should be able to:
PH 1.6 Describe principles of pharmacovigilance and ADR reporting systems.[3]

Definition: Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.

It deals with the epidemiologic study of adverse drug effects.

The aim of pharmacovigilance is to ensure safe and rational use of medicines. Since clinical trials are done on a limited number of patients, many potential adverse effects go undetected. Hence reporting adverse reactions is the **duty of all medical professionals**. The adverse reactions reported and related data is collected and assessed by the pharmacovigilance system consisting of ADR reporting centres, regional and national pharmacovigilance centres which in turn report to the Uppsala Monitoring Centre at Sweden.

In India, the Central Drugs Standard Control Organization (CDSCO) in collaboration with Indian Pharmacopoeia Commission, located at Ghaziabad has initiated a pharmacovigilance programme of India **(PVPI)**, which consists of peripheral, regional and zonal centres for coordinating the activity. Under the ADR monitoring centre, various medical colleges and hospitals function to report ADRs. The data collected is uploaded into the pharmacovigilance software **Vigiflow**. Effective pharmacovigilance activity and awareness of toxic effects of drugs has resulted in the withdrawal of several potential toxic drugs from the market (Fig. 4.2).

ADR analysis: The reported ADRs are assessed to know whether they were actually drug induced. Several scales are available for the purpose but the most preferred are the Naranjo's scale and WHO scale.

Haemovigilance: Adverse reactions associated with transfusion of blood and blood products is haemovigilance. It also needs to be reported through the software 'haemovigil'.

Materiovigilance is ADRs to biological devices.

Medication errors: Medication errors are errors that occur in the process of prescribing, dispensing and administration of drugs. They could occur at the level of doctors, pharmacists, nurses or patients. Adequate care should be taken to avoid them.

Look-alike Sound-alike (LASA) Drugs

LASA drugs are also referred to as **SALA** (sound-alike look-alike) drugs particularly in India! These are drugs which have similar names or look similar due to packaging and should be dealt with extra care since they can be confusing and result in medication errors. Drugs like clotrimazole and cotrimoxazole are likely to be easily mistaken. Precautions are to be taken to avoid such errors like writing the names in capital letters. Several brand names also sound similar. Look-alike drugs should be stored in separate racks or cupboards to avoid dispensing errors.

Some examples of sound-alike drugs are:

Amiodarone	–	Amantadine
Amlodipine	–	Amiloride
Buspirone	–	Bupropion
Cycloserine	–	Cyclosporine
Hydroxyzine	–	Hydralazine
Lamotrigine	–	Lamivudine

Over-the-counter (OTC) Drugs

Drugs which are considered safe for use by general public without a prescription are called 'over-the-counter' drugs or non-prescription drugs. Directions for their use can be easily understood by the patients and are mentioned on the information sheet dispensed along with the drugs. Drugs that can be dispensed as OTC drugs are chosen by the regulatory agency and include drugs for common ailments like cough, influenzae, diarrhoea, vomiting, allergy and gastric hyperacidity. However, OTC drugs also carry the risk of side effects and inappropriate use. History of OTC drug intake is essential since they could result in adverse effects and drug interactions.

Off-label use of drugs: When a drug is used for indications other than the approved ones, it is called 'off-label' use of drugs. The drug may be used for a different disease, indicated by a different route of administration or in a different dose. Examples: Clonidine is also used in attention deficit hyperactivity disorder. Diazepam from ampoule for injection is used rectally in febrile convulsions and status epilepticus. Azathioprine used topically for psoriasis, atopic dermatitis; erythromycin for gastroparesis, SSRIs for fibromyalgia and pathologic gambling.

COUNTERFEIT DRUGS

Counterfeit drugs are fake drugs. They are drugs or pharmaceutical products that contain inadequate dose or the inappropriate drug itself. The labelling, packaging or other information provided may be inappropriate with the intention of misleading the consumers. These spurious drugs may contain hazardous adulterants, beyond expiry date drugs, fake brand name drugs, or substandard drugs. Such counterfeit drugs can be harmful to the consumers.

DRUG INTERACTIONS

Competency achievement: The student should be able to:

PH 1.8 Identify and describe the management of drug interactions.[4]

Definition

Drug interaction is the alteration in the duration or magnitude of the pharmacological effects of one drug by another drug.

When two or more drugs are given concurrently, the response may be greater or lesser than the sum of their individual effects. Such responses may be beneficial or harmful. For example, a combination of drugs is used in hypertension—hydralazine + propranolol for their beneficial interaction. However, drug interactions may also result in severe toxicity. Such interactions can be avoided by adequate knowledge of their mechanisms and by judicious use of drugs. Some important drug interactions are mentioned in Appendix 1.

Site

Drug interactions can occur:

1. *In vitro* in the syringe before administration—mixing of drugs in syringes can cause chemical or physical interactions—such drug combinations are incompatible in solution, e.g. penicillin and gentamicin should never be mixed in the same syringe.
2. *In vivo,* i.e. in the body after administration.

Pharmacological Basis of Drug Interactions

The two major mechanisms of drug interactions include pharmacokinetic and pharmacodynamic interactions.

Pharmacokinetic Mechanisms

Alteration in the extent or duration of response may be produced by influencing absorption, distribution, metabolism or excretion of one drug by another.

Absorption of drugs from the gut may be affected by:

1. *Binding:* Tetracyclines chelate iron and antacids resulting in reduced absorption. Cholestyramine is a bile acid binding resin which also binds many drugs.
2. *Altering gastric pH:* Antacids raise gastric pH and interfere with the absorption of drugs like iron and anticoagulants.
3. *Altering GI motility:* Atropine and morphine slow gastric emptying and delay the absorption of drugs. Purgatives reduce the absorption of riboflavin.

Distribution: Competition for plasma protein or tissue binding results in displacement interactions, e.g. warfarin is displaced by phenylbutazone from protein binding sites.

Metabolism: Hepatic microsomal enzyme induction and inhibition can both result in drug interactions (*see* page 31), e.g. phenytoin, phenobarbitone, carbamazepine and rifampicin are enzyme inducers while chloramphenicol and cimetidine are some enzyme inhibitors.

Excretion: When drugs compete for the same renal tubular transport system, they prolong each other's duration of action, e.g. penicillin and probenecid.

Pharmacodynamic Mechanisms

Drugs acting on the same receptors or physiological systems result in additive, synergistic or antagonistic effects. Many clinically important drug interactions have this basis. Examples are:

- Atropine opposes the effects of physostigmine.
- Naloxone antagonises morphine.
- Antihypertensive effects of β-blockers are reduced by ephedrine or other vasoconstrictors present in cold remedies.
- Many diuretics produce hypokalaemia which potentiate digitalis toxicity.
- Organic nitrates (used in angina) act by increasing cGMP activity. Sildenafil inhibits phosphodiesterase which inactivates cGMP and thereby potentiates the effects of nitrates. Hence the combination can cause severe hypotension and even deaths have been reported.

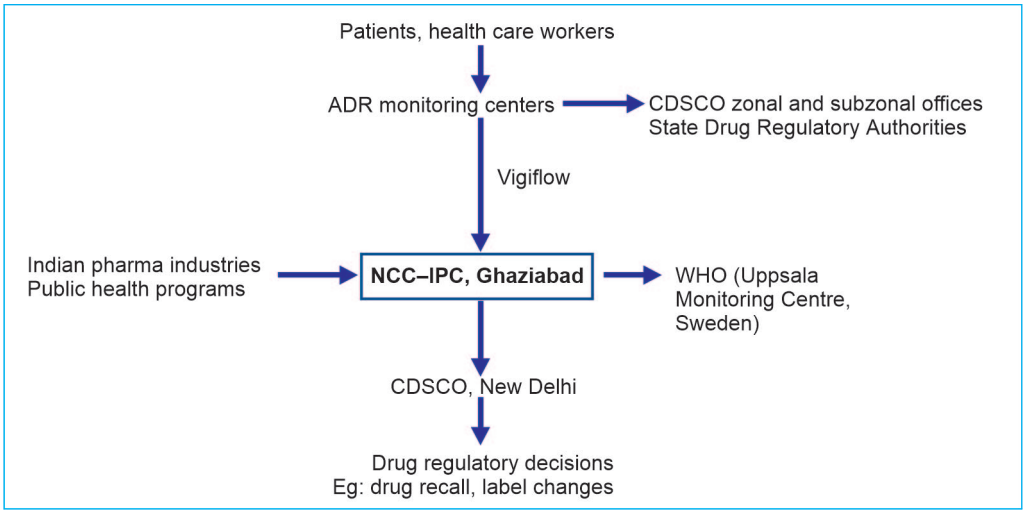


Fig. 4.2: Flow of ADR information and working of PvPI
NCC: National Co-ordination Centre, PvPI: Pharmacovigilance Program of India

- Aspirin inhibits platelet aggregation and enhances the risk of bleeding due to oral anticoagulants like warfarin.
- Many antihistamines produce sedation which may be enhanced by alcohol intake.

Drug–Food Interactions

Simultaneous intake of food and drugs could result in some interactions. Presence of food itself interferes with the absorption of several drugs like rifampicin, roxithromycin which need to be given on an empty stomach.

- Drugs also interact with constituents of food like milk (tetracycline, iron) and reduce the bioavailability of these.
- Tender coconut water and fruits (e.g. sweet lime) rich in potassium can add up to the hyperkalaemia caused by ACE inhibitors.
- Cheese reaction—consumption of tyramine-containing foods like cheese, beer, wines, yeast, buttermilk and fish by patients receiving MAO inhibitors results in hypertension—termed cheese reaction. Inhibition of MAO by drugs leads to raised tyramine levels which displaces NA from the adrenergic nerve terminals resulting in hypertension.
- Grapefruit is an enzyme inhibitor and thereby raises the levels of phenytoin.

Databases for drug interactions: Since memorizing drug interactions is a great challange, help of software may be needed often to ensure patient safety when multiple drugs are used. Many softwares are available for the purpose on the internet some of which are free.

[1–4] From Medical Council of India, *Competency based Undergraduate Curriculum for the Indian Medical Graduate*, 2018;1:136–144.

Drug Nomenclature, Drug Development, Drug Regulations, Essential Medicines, Prescriptions and Related Topics

CHAPTER 5

Competency achievement: The student should be able to:
PH 1.9 Describe nomenclature of drugs, i.e. generic, branded drugs.[1]

DRUG NOMENCLATURE

A drug can have four names:

1. **Code name:** When a new drug is synthesized/discovered, it is given a **code name** at the time of development. It consists of letters and numbers like AMG 785. Once the drug is approved for use, the code name is no more used (Table 5.1).

2. **Chemical name:** The *chemical name* gives the chemical description of the drug, e.g. 3, (10, 11-dihydro-5H-dibenz (b,f)-azepin-5-yl) propyldimethylamine. This is lengthy, complex and unsuitable for prescribing.

3. **Generic name (non-proprietary)** is given by a competent recognized official agency like WHO and is internationally accepted, i.e. the drug has the same generic name all over the world. It is called International Non-proprietary Name (INN). The INN system came into effect in 1953 and was initiated at a resolution by World Health Assembly. It gives a clue to the class of the drug, because drugs in a group sound similar as they end with the same letters, e.g. propranolol, atenolol, esmolol, metoprolol—all are β-blockers and cimetidine, ranitidine, famotidine, and roxatidine are all H_2 receptor blockers. It is convenient and the drug is sometimes cheaper when prescribed by generic name. The nonproprietary name of the above example given under chemical name is imipramine.

4. **Brand name (proprietary)** is the trade name given by the manufacturer. Hence each drug may have many brand names, e.g. Crocin, Metacin, Pacemol, Calpol are different brand names of paracetamol. The main advantage in using brand name is the consistency of the product especially bioavailability. Hence, for drugs with low therapeutic index like digoxin and antiepileptics, prescribing the same brand name is beneficial. Certain guidelines are laid by the concerned authorities in giving brand names to pharmaceutical products in each country and the name has to be approved by the authority before being marketed by the company.

DRUG DEVELOPMENT

Competency achievement: The student should be able to:
PH 1.64 Describe overview of drug development, Phases of clinical trials and Good Clinical Practice.[2]

The last few decades have seen the development of several new drugs which have

Table 5.1: Drug names

Code name	*Generic name*	*Chemical name*	*Brand names*
RU-486	Mifepristone	11beta17alpha(1propynyl)estra-4,9-dien-17beta-01-3-one	UNDO, MT-PILL, UNWANTED

revolutionised the practice of medicine. The discovery and development of a new drug is a time-consuming and expensive procedure.

A new drug may be identified by the following processes:

1. Chemical modification of a known drug.
2. Random screening of natural and synthetic chemicals to detect useful activity.
3. Rational drug designing based on the chemical structure.

After identification, the structure of the new compound and its purity are determined by the analytical chemist. The compound is screened for the presence of any useful biologic activity by a series of tests like bioassays, molecular and cellular studies, followed by tests in whole animals. If the compound is found to be promising, then it is subjected to preclinical evaluation in animals and then clinical trials in humans.

Preclinical Evaluation

When a new compound is synthesized or discovered, it is first subjected to preliminary screening. In the first stage, the target chemical is identified. The next step is to develop the lead compound which involves cloning of the target protein, identifying its functional activity and then subjecting it to high throughput screening.

Clinical Trials

When the drug is found to be reasonably safe in animals, it is subjected to clinical trials in human beings after obtaining permission from the regulatory agency. Clinical trials are conducted to compare the therapeutic efficacy of a new drug with an existing drug or a placebo.

Good clinical practice: For the conduct of clinical trials, certain regulatory guidelines are laid down in order to ensure safety of the subjects and transparency in the trial activities. The guidelines for good clinical practice and ethics are formulated by certain regulatory bodies. For the conduct of clinical trials in India, the guidelines by International Conference on Harmonization (ICH) Food and Drug Administration USA (USFDA), New Drug and Clinical Trials rules (NDCT-2019), Good Clinical Practice (GCP) guidelines of India, and the guidelines by WHO and ethical guidelines by Indian Council of Medical Research (ICMR) are followed. These guidelines aim to protect human rights and ensure that authentic and credible clinical trial data is generated.

Ethical clearance: After obtaining permission from the concerned regulatory authorities to conduct the trial in a given setting, permission should be obtained from the local institutional ethics committee (IEC) or institutional review board (IRB). The IEC looks into the ethical aspects of the trial and ensures that the trial is conducted ethically and the rights of the study participants are protected.

Informed consent: For enrolling a subject into a clinical trial, he/she should be informed in detail about the trial including the risks involved and the subject should willingly consent to participate in the study. He should sign the informed consent form and should also be made aware that he is free to withdraw from the study whenever he wants to. This is to ensure that the participation in the study is purely voluntary and not by force.

Phases of Clinical Trials

Clinical trials are generally conducted in 4 phases though phase 0 is also included in some situations (Table 5.1):

Phase 0: Phase 0, also called **microdosing**, is a recent approach in clinical trials to cut cost in drug development. It is conducted in a small number of subjects (10–15) for a short duration (<7 days). A very small dose is used to evaluate the pharmacodynamics and pharmacokinetics in human beings (the first exposure in humans) and are exposed to the

Table 5.1: Phases of clinical trials

Phases	*Number of subjects*	*Objectives*	*Conducted by*
Phase 0	10–15	Explore pharmacokinetics and pharmacodynamics	Clinical pharmacologist
Phase I	20–50 normal volunteers	To establish safety, to know biological effects, pharmacokinetic profile and to design a safe dose	Clinical pharmacologist
Phase II	100–300 patients	To establish efficacy, detect adverse effects and pharmacokinetics	Clinical pharmacologists and clinical investigators
Phase III	250 to >1000 selected patients	To establish efficacy, safety, to identify latent side effects, tolerance, design ideal dose-range, and to compare with existing drugs	Clinical investigators
Phase IV (Post-marketing surveillance)	2000 to >10,000 patients	Long-term safety and efficacy; to identify other possible therapeutic uses	Medical practitioners

drug for a short period. Analysis is done by highly sensitive methods like accelerated mass spectrometry and positron emission tomography (PET).

Phase I: Less than 50 normal healthy volunteers are given the drug to establish safety, to know the actions, determine pharmacokinetic profile and to design a safe dose for further use.

Phase II: If phase I is successful, the compound undergoes phase II evaluation in order to establish efficacy, to detect any adverse effects, appropriate dose and detailed pharmacology of the chemical in 100–300 patients suffering from diseases for which the drug under trial has therapeutic prospects.

Phase III: If the phase II establishes that the drug is useful and generally safe, phase III clinical trials are undertaken. A large number of selected patients is given the drug to establish the benefits of the drug in the target disease, to identify the latent side effects, susceptibility to tolerance and to design ideal dosage regimen for different groups of patients.

Phase IV: Postmarketing surveillance—If phase III studies are satisfactory, the new drug is marketed. Since the earlier phases involve a relatively smaller number of patients (3000) for short periods (<1 year), they cannot be expected to provide full safety information. Thus postmarketing surveillance is done for systematic detection and evaluation of long-term safety of the drug. It is done by collection and evaluation of data based on information sent by medical practitioners prescribing the drug. Phase IV trials are thus conducted by medical practitioners.

Clinical Trials Registry

With the progress in research, several new molecules have been synthesized all over the world. With the growing public awareness about drugs and diseases, information on newer drugs and upcoming medication is sought both by doctors as well as public. In order to make the drug development transparent, accountable and data accessible, **Clinical Trial Registry of India (CTRI)** has

Meta-analysis

Data from several clinical trials or studies are combined and the results are analysed (each study should have followed the same procedure). This is known as meta-analysis and helps to obtain more accurate results as a larger number of subjects are considered.

been set up by the joint efforts of Indian Council of Medical Research (ICMR), Department of Science and Technology (DST) and World Health Organisation (WHO). All clinical trials being conducted in India should be registered in CTRI. Though the registration is voluntary and free of cost, registration has several benefits for the investigators, like—it is possible to publish data from clinical trials because, for the publication of data from clinical trials, CTRI registration is required. The details registered are freely accessible to all including general public.

Orphan Drugs

Orphan drugs are drugs to be used for prevention and treatment of rare diseases. Such drugs are not readily developed and marketed because they are not profitable to the manufacturer. Example: Acetylcysteine used for paracetamol overdosage, 4 methylpyrazole in poisoning due to methanol or ethylene glycol, 4-aminosalicylic acid in the treatment of ulcerative colitis. Such rare diseases are also called **orphan diseases**. The Orphan Drugs Act provides incentives to the drug manufacturers for the development of orphan drugs.

DRUG INFORMATION SOURCES

Information on drugs can be obtained by:

- *Primary source:* Original research published in journals and information from clinical trials.
- *Secondary source:* Data from research analysed, compiled and published, e.g. in medline, index medicus, etc.
- *Tertiary source*—include drug compendia.

Drug Compendia

Books that are sources of information on drugs, i.e. pharmacopoeia and formularies are together known as drug compendia. The third one is e-source, i.e. the medline

1. **Official compendia**
   - Pharmacopoeia
   - Drug formulary
2. **Non-official compendia**
   - Textbooks
   - Journals
   - Periodicals
3. **Medline**

1. Official compendia are recognized by the government of that country as 'legal standard'.

Pharmacopoeia: Pharmacopoeia is the official publication of a list of drugs and medicinal preparations. In Greek 'Pharmacon' means drug and 'poeia' is to make. It contains a list of drugs and related substances that are approved for use, their source, formulae and other information needed to prepare the drugs, their physical properties, tests for their identity, purity and potency. Each country may follow its own pharmacopoeia. We thus have Indian Pharmacopoeia, British Pharmacopoeia, United States Pharmacopoeia, USSR and Japanese Pharmacopoeia. The European Pharmacopoeia was published by the Public Health Committee and the European Pharmacopoeia Commission. The International Pharmacopoeia is published by WHO in many languages like English, French, Spanish and Russian.

The first pharmacopoeia of India was published in 1868. But later under the British rule, the British Pharmacopoeia was followed. After independence, a committee was set up and Indian Pharmacopoeia was released in 1955. Experts from pharmaceutical industry, drug control laboratories and research and teaching institutions helped the committee.

Pharmacopoeia is revised at regular periods to delete old, useless drugs and to include newly introduced ones.

Drug formulary: The National Formulary contains information on therapeutically used formulations. It is prepared by the National Formulary Committee set up by the Ministry of Health, Government of India. Expert opinion

is also taken from medical associations, hospitals, teaching institutions and pharmaceutical industry in preparing this book.

2. Non-official compendia: These are books other than the official compendia and include textbooks of pharmacology, journals and periodicals.

3. Medline: Medline or medical literature analysis and retrieval system online is a literature database of life sciences and biomedical information.

PHARMACOECONOMICS

Competency achievement: The student should be able to:
PH 1.60 Describe and discuss pharmacogenomics and **pharmacoeconomics**.[2]

Pharmacoeconomics is the science that compares the cost of various treatment modalities to the outcome. It helps to know which treatment is less expensive and effective. This information will be useful to effectively use the funds and resources to improve healthcare. It aims to effectively use the resources to improve healthcare and also pays attention to quality of life in healthcare policies—'value-for-money' approach.

In recent years extensive research in **pharmacoeconomics** is undertaken.

Goals of pharmacoeconomics research are:

1. To know which healthcare alternatives provide the best outcome for the money spent
2. To improve allocation of funds

Whenever possible the doctor needs to consider cheaper and effective alternatives for the treatment of all ailments. Pharmacoeconomics studies aim to provide such information.

Types of Pharmacoeconomics Analysis

1. *Cost minimization analysis:* This aims to find out the best treatment alternative with minimum cost. For example, comparing 2 generic drugs.
2. *Cost effectiveness analysis:* In this the health benefits can be measured in units and is the most commonly used pharmacoeconomics analysis. It compares therapies where the outcome is common and can help in the identification of a preferred choice among alternatives. For example, number of years of life prolonged following treatment.
3. *Cost-benefit analysis:* This compares the cost and the outcome of alternative regimens. For example, cost and outcome of surgery vs pharmacotherapy for coronary heart disease.
4. *Cost utility analysis:* Here the outcome of treatment is measured in terms of quality of life or QALY (quality adjusted life years). For example, comparing the quality of life while using two different antihypertensives.

Pharmacogenomics—see page 54.

CHRONOPHARMACOLOGY

Chronopharmacology deals with the correlation of drug effects to the circadian rhythm.

Association of Diseases with Circadian Rhythm

- Higher incidence of MI and stroke is seen early in the morning.
- Intraocular pressure variations are seen throughout the day.
- BP is highest during the afternoon and gradually decreases to reach lowest levels at night.
- Symptoms of allergic rhinitis is worst in the morning.

Application of Chronopharmacology in Therapeutics

Morning: Glucocorticoids and testosterone are administered in the morning to mimic the natural secretion.

Evening: Statins are given in the evening.

Night:

- Aspirin is administered at night to prevent platelet aggregation which is more likely in the morning.
- For allergic rhinitis, antihistamines are given at night to prevent allergic response the next morning.
- Diuretics are given in the morning to reduce hypokalemia.

ESSENTIAL MEDICINES

Competency achievement: The student should be able to:
PH 1.59 and 3.7 Prepare a list of essential medicines for a healthcare facility.[1]

WHO has compiled a list of drugs that is required to meet the primary healthcare needs of majority of the population and are called essential drugs. Essential medicines have been defined by WHO as those that satisfy the healthcare needs of majority of the population and should, therefore, be available at all times in adequate amounts and in the appropriate dosage forms. The original list has undergone revisions and updating from time to time to meet the changing requirements. Based on the WHO guidelines for selection of essential drugs and by referring its model list, each country puts forth its national list of essential drugs.

- Adoption of the list has resulted in greater coordination in healthcare development.
- The list serves as a guideline for indenting and stocking essential drugs.
- The concept has also helped in the development of national formularies.
- A short list is compiled for community health workers to aid in providing primary healthcare.
- The use of essential drug list has also emphasised the need for drug research and development, e.g. safety and efficacy of a new drug should be established for it to be included in the essential drugs list.

India's first National **Essential Medicines** List consisting of about 300 drugs was formulated in 1996. 21st model list of essential medicines was brought out by WHO in June 2019.

RATIONAL DRUG USE

Once a patient is diagnosed to have a particular disease and needs to be treated with drugs, the specific **therapeutic objective** should be defined. For example, in hypertension, the objective is to bring down the BP to a particular level in order to prevent complications of prolonged hypertension. Once the objective is clear, the **choice of drugs** should be made. Various aspects should be considered while choosing the drug. When many drugs are available for the treatment of the particular condition, the right choice should be carefully made. For example, hyperacidity and mild gastritis may be managed with antacids. When not controlled, an H_2 receptor blocker like ranitidine helps. Only more severe cases require to be treated with omeprazole. Patient factors including age, presence of other diseases, renal and liver function, other drugs being administered and cost of therapy should be considered. Newer drugs are all expensive. When less expensive older drugs are available, they should be preferred to the newer ones. Though human insulin is the rational choice for all diabetics who need insulin, majority of patients in the developing countries like India cannot afford such an expensive medication for the rest of their lives. Hence conventional insulins are still preferable in them—unless contraindicated.

The **dose and the duration** of treatment should be determined. When long-term treatment is required, the regular review and monitoring of treatment should be planned. The therapeutic end point should be defined.

When a **combination of drugs** is to be administered, the guidelines like better

therapeutic benefit, avoiding drugs with overlapping adverse effects and cost of therapy should be borne in mind. Equally important is to avoid irrational combination of drugs. The flourishing drug industry often comes out with absurd combinations of drugs. They serve no useful purpose, are more expensive and unnecessary, but are vigorously promoted and unfortunately often prescribed by doctors. Some such examples are:

1. *Amoxicillin (250 mg) with cloxacillin (250 mg):* Combined with the view that cloxacillin can destroy the penicillinase producing *Staphylococcus aureus* (PPSA) while amoxicillin can help, if the infection is with other bacteria. But, in fact, if the infecting organism is PPSA, 250 mg cloxacillin is an underdosage. If it is not PPSA, 250 mg of amoxicillin is an underdosage. It should be noted that cloxacillin is not an efficient antibiotic in infections other than PPSA while amoxicillin is of no use in PPSA. Therefore, the combination is totally irrational.
2. *Ibuprofen with paracetamol:* Either of them can be given based on the requirement. Combination serves no useful purpose.
3. *Diclofenac + nimesulide:* Either of them can be given based on the requirement. Combination serves no useful purpose. Nimesulide is now banned in most of the countries.
4. *Ciprofloxacin + tinidazole:* The combination is used in diarrhoea. It is claimed that it helps in diarrhoea due to both gram-negative bacteria and amoeba. In reality, the diarrhoea is due to either of the organisms and not both. Using the combination only exposes the patient to the risk of toxicity from the other antimicrobial agent and also adds to the cost of therapy.

P-DRUGS

Pharmacology has grown to an extent where it extensively taxes the memory of any human brain to remember all the drugs described in the books. In daily practice, however, a physician needs to be proficient in using fewer drugs (40–60). For any illness, if there are many drugs in a group, the physician may choose some primary drugs which need to be used routinely and be thorough with their pharmacology. Such a choice of drugs called **P** or **personal drugs** are used to prescribe regularly. The doctor needs to also know the dose, formulations, duration of treatment, drug interactions and precautions in using such P-drugs.

P-treatment: For any given illness, the treatment of first choice is the P-treatment. It depends on the therapeutic objective, safety, efficacy and cost of treatment.

When a patient has to be treated with drugs, the question of 'selection of the right drug' arises. WHO provides certain guidelines for **good prescribing**. When a patient is seen by a doctor, the steps of approach would be to establish the diagnosis and then to specify the therapeutic objective. For example, if an infection is to be treated, the objective would be to cure the infection; in some of the cancers, the objective would be palliation. Having defined the objective, the P-drugs have to be chosen and their suitability for the particular patient verified. The treatment is then started where caution is to be taken to avoid overprescribing or under treatment. The strength, precautions for use, right dose for the right length of time and the relevant information to the patient regarding the drugs including its mode of action, adverse effects and dosage instructions are to be given. Once the patient is on treatment, monitoring is required. **Monitoring** is done to ensure if the treatment was effective, safe, to look for any adverse effects and if the compliance was good. Monitoring may be passive where the patient is instructed about the outcome of treatment and is told what to do if there is toxicity or no response. Active monitoring may be needed for most conditions where the doctor has to check, if the treatment was effective.

Hence, every doctor needs to do his best for his patients with the right drug, the right

dose and for the right duration of treatment based on his judgement and guided by his experience. He has to update his knowledge regularly and revise his list of P-drugs from time to time rather than blindly following the directions of the seniors in his field.

DRUG REGULATIONS

Competency achievement: The student should be able to:
PH 1.63 Describe drug regulations, acts and other legal aspects.[4]

In 1940, The Drugs Act was passed to control the manufacture, sale and distribution of allopathic drugs. Later the Act was amended several times and it now also includes Ayurvedic, Unani, Siddha and Homeopathic drugs. An amendment was made in 1962 to include cosmetics and the title changed to the **Drugs and Cosmetics Act.** Under the Act, clear rules have been framed for the import, manufacture, sale, labelling and packing of drugs.

Drug schedules: Some important schedules controlling manufacture, distribution and sale of drugs in India are given in Table 5.2.

Some Recent Concepts in Pharmacology

Reverse pharmacology is the science of integrating drug development by subjecting clinical hits to experimentation to know their mechanism of action and other pharmacological aspects. The safety of many of the routinely used traditional medicines like ayurvedic drugs are well known. They are subjected to experimentation to scientifically detect and prove their therapeutic benefits. It helps to understand the mechanisms of action and other pharmacological aspects of these drugs. Here regular approach of the drug discovery course from 'lab to clinics' is reversed to 'clinics to labs'. Examples of drugs which were successfully proved to be useful are—artemisinin and reserpine.

- *Conventional method*
  Molecule → mice → man
- *Reverse pharmacology path*
  Man → mice → molecule

Translational medicine is the application of laboratory research to patient care, i.e. from the bench to bedside. Translational medicine involves closer collaboration between the industry and academics, that is, transfer of advances in basic scientific research to treatment of diseases in a shorter time.

PRESCRIPTION WRITING

Competency achievement: The student should be able to:
PH 1.10 Describe parts of a correct, complete and legible generic prescription. Identify errors in prescription and correct appropriately.[5]

The Prescription is a written order by a physician to the pharmacist to prepare and/or dispense specific medication for a specific patient. A specific pattern should be followed in writing prescriptions, in order to avoid errors and to safeguard the interests of the patient. Moreover, the fact that it is a medicolegal document makes it all the more important to be accurate and precise.

The following points should be remembered in writing a prescription:

1. The writing should be legible. The drug names should be in capital letters so that they are legible.
2. Indelible ink should be used in writing.
3. Abbreviations should be avoided.
4. Generic names of drugs should be written below the brand names.
5. In writing quantities, decimals should be avoided; when inevitable, zero should be used—0.1 for .1.
6. Less than 1 g should be written as milligrams, e.g. 200 mg and not 0.2 g. No abbreviation should be used for micrograms and units.
7. Blank space should be avoided between direction and the signature of the doctor. If blank space is present, it should be striked off to avoid misuse of the space to obtain drugs illegally.

Table 5.2: Important drug schedules

Schedule	*Features*	*Examples*
Schedule H drugs—to be sold under "prescription only"	• Warning to be given on the label: Schedule H drug. Warning: To be sold on the prescription of registered medical practitioner only • Symbol R_x should be printed prominently on the left hand top corner of the label • If the drug is covered under Narcotic Drugs and Psychotropic Substances Act, symbol NR_x should be printed instead of R_x • The rules for sale are same as for schedule X drugs	Acyclovir Alprazolam Amitriptyline Atenolol Azathioprine Bacampicillin Barbiturates Antibiotics
Schedule X: Psychotropic drugs	• The label should contain the warning: "Schedule X drug" • Symbol X R_x in red letters on left hand top corner • Warning: To be sold on presciption of a registered medical practitioner only • Schedule X drugs should be stored under lock and key • Drugs should not be dispensed more than once unless such an instruction is given in the prescription • No substitute or alternative drug should be given • The prescription should be in duplicate and a copy should be retained for at least 2 years • On the cash bill, the purchaser's signature should be taken.	Amphetamine Barbiturates Methaqualone Glutethimide
NDCT-2019	Describes requirements and guidelines for new drug and clinical trials	
Other important drug schedules:		
Schedule C	Includes biological and special (intravenous) products Druggists require separate license for sale of these drugs	Insulin, adrenaline
Schedule E	Includes poisons and drugs under Ayurvedic, Siddha and Unani systems of medicine. It applies to the storage and sale of such drugs.	
Schedule F, F1	Include vaccines and sera	
Schedule G	For these drugs, label should have the warning—'Caution: It is dangerous to take this preparation except under medical supervision'. Containers should be labelled in red bottles against white background	Ethosuximide; anticancer drugs like bleomycin; hormones antidiabetics like insulin, glibenclamide
Schedule S	Prescribes standards for cosmetics	

PARTS OF THE PRESCRIPTION

1. Date of writing the prescription.
2. Address of the prescriber—preferrably prescriptions are written on the letter pad with doctor's name and address printed at the top.
3. Name, age, sex and address of the patient.
4. Superscription—the symbol R_x meaning 'take thou' is also considered as an invocation to the Greek Gods of healing—Jupitor and Horus.
5. Drug name and strength. This is the body of the prescription—also called inscription. Abbreviations should never be used.
6. Directions to the pharmacist (subscription)—consists of instructions for compounding if any and the quantity to be supplied.

Model Prescription

Dr Vaidya July 10, 2001
Highland
Mangalore Telephone no.....

Ramu, Male, Age: 35 years
Address: No. 7, Kankanady
Mangalore 575002

R_x
Tab ROXITHROMYCIN 150 mg
Dispense 10 tablets

Directions: Take 1 tab orally twice a day, 30 minutes before food for 5 days.

Signature
Regn. No.

Some commonly used Latin abbreviations in prescriptions

Abbreviation	*Latin derivation*	*Meaning in English*
o.d.	onus in die	once a day
b.d.	bis in die	twice a day
b.i.d.	bis in die	twice a day
t.i.d.	ter in die	three times a day
t.d.s.	ter die sumendum	three times a day
q.i.d.	quarter in die	four times a day
h.s.	hora somni	at bedtime
stat	statim	at once
s.o.s.	si opus sit	if necessary
q.s.	quantum sufficit	a sufficient amount
p.o./po	per os	by mouth
ung	unguentum	ointment
caps	capsula	capsules
Tab	Tabella	tablet
a.c.	ante cibum	before food

7. Directions to the patient—should be clear and should indicate the quantity, frequency, time, route of administration and other information relevant to the preparation. If a drug is meant only for external application or needs to be shaken well or mixed before using—such instructions should be mentioned.
8. Signature of the prescriber—the prescriber should sign along with registration number.

TYPES OF PRESCRIPTIONS

1. *Precompounded prescription*—orders for a drug manufactured by a pharmaceutical company, has a trade name and is available for use.
2. *Compounded or extemporaneous prescription*—the physician directs the pharmacist to compound a preparation. The ingredients, their quantity and the form of preparation (like mixture, powder or ointment) is chosen by the physician and instructed accordingly.

[1–5] From Medical Council of India, *Competency based Undergraduate Curriculum for the Indian Medical Graduate*, 2018;1:136–144.